BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY AUGUST 19 1961

O STATE
VERSITY
EP 6 1961

RECEIVED

HEALTH CENTER LIBRARY

TABLE OF CONTENTS

Diuretics and the Eye DOROTHY ADAMS CAMPBELL, M.B., F.R.C.S. 467

A New Variant of Human Intersex with Discussion on the Developmental Aspects PRABHAKER N. SHAH, M.D., F.C.P.S.(Vet.), S. N. NAIK, B.SC., M.SC., D. K. MAHAJAN, M.SC., M. J. DAVE, M.SC., and J. C. PAYMASTER, F.R.C.S.Ed. 474

Corrosion of Orthopaedic Implants JOHN T. SCALES, M.R.C.S., L.R.C.P., G. D. WINTER, B.SC., and H. T. SHIRLEY, B.SC., A.R.C.S. 478

Reversed-ear Syndrome and the Mechanism of Barotrauma ANTONY JARRETT, M.SC., M.B. 483

Plasma Cholesterol Levels in New Zealand J. D. HUNTER, M.B., M.R.C.P., M.R.A.C.P., and L. C. K. WONG, M.SC. 486

Carcinoma and Cushing's Syndrome J. R. BILLINGHURST, B.M, M.R.C.P., A. K. THOULD, M.D., M.R.C.P., O. P. GALPIN, M.B., M.R.C.P., and J. M. HINTON, B.M. 490

Acute Carbon Tetrachloride Poisoning J. K. DAWBORN, M.B., M.R.A.C.P., MARY RALSTON, M.B., D.C.P., M.C.P.A., and S. WEIDEN, M.SC., Ph.D. 493

PRELIMINARY COMMUNICATIONS

Adenovirus and Intussusception. P. S. GARDNER, M.D., Dip.Bact. 495

MEDICAL MEMORANDA

Case of Mesenteric Reticulosarcoma Associated with Gluten-sensitive Steatorrhoea. C. N. BEST, M.B., M.R.C.P.Ed., and P. B. COOK, M.D., M.R.C.P., D.P.H. 496

Extraperitoneal Fibrosis. STEPHEN POWER, M.S., F.R.C.S. 498

BOOK REVIEWS 499

GENERAL ARTICLES AND NEWS

Scope and Functions of an Airline Medical Service, with Particular Reference to B.O.A.C. K. G. BERGIN, M.D., D.P.H., F.R.Ae.S. 508

Hospital and Medical School Design 512

Sir Almroth Wright, 1861-1947 516

To-day's Drugs 518

APPROVED NAMES 516

NEW APPLIANCES 516

OBITUARY 525

MEDICO-LEGAL 527

MEDICAL NOTES IN PARLIAMENT 528

UNIVERSITIES AND COLLEGES 528

VITAL STATISTICS 529

MEDICAL NEWS 530

BIRTHS, MARRIAGES, AND DEATHS 532

QUESTIONS AND COMMENTS 533

LEADING ARTICLES

Early Maturing and Larger Children 502

Narcolepsy 503

Benign Hodgkin's Disease 504

ANNOTATIONS

The Continuing Problem of Gonorrhoea 504

Carcinoma and Cushing's Syndrome 505

Mishap at a Reservoir 506

Epilepsy and Driving Licences 506

Barotrauma of Auditory Canal 507

CORRESPONDENCE

The Englishman's Height. C. O. CARTER, M.R.C.P. 518

Attendance at V.D. Clinics. C. S. NICOL, M.D.; J. L. FLUKER, M.D. 518

Chemotherapy of Urinary and Intestinal Infections. G. A. STANTON, M.B. 519

Radioisotopes in Tumour Location. LINDSAY SYMON, F.R.C.S. 519

Abdominal Wound Dehiscence. A. W. G. WEIR, M.R.C.O.G. 520

SUPPLEMENT

Full Contents on First Page of Supplement

Joint Consultants Committee 125

Hospital Drug Costs 125

N.H.S. Superannuation Scheme 126

Correspondence:

Doctors and the State. J. A. GORSKY, L.M.S.S.A 127

Doctors in the Armed Forces. T. COCHRANE, O.B.E. 127

CORRESPONDENCE—*contd.*

Spontaneous Rupture of Colon. S. M. FEINBERG, M.B. 520

Occupational Health Services. L. J. HAYDON, M.B. 520

"Functional" Disorders. J. S. NORELL, M.B. 521

Malaria and Glucose-6-phosphate Dehydrogenase. A. C. ALLISON, B.M., and D. F. CLYDE, L.M.S. 521

Apnoea, Hypertension, and Conjunctival Oedema. JOHN L. WEBSTER, D.Obst. R.C.O.G. 522

Suicide with Thioridazine. J. B. ENTICKNAP, M.D., and B. GORDON, D.P.M. 522

Intraperitoneal Haemorrhage from Fibroids. C. H. J. REY, F.R.C.S. 523

Fusion of Labia Minora. G. W. LEWIS, M.D.; C. H. DE BOER, F.R.C.S., and I. GOTTLIEB, L.R.C.S.Ed. 523

Psychopaths Aged Over 25. K. C. BAILEY, D.P.M. 524

Staphylococcal Infections. B. BENDKOWSKI, M.D. 524

Panic Immunization. A. W. FRANKLAND, D.M. 524

Plague Documents. W. RADCLIFFE, M.B. 524

Latent Brucellosis in Farmers. IAN MCWHINNEY, M.D., and A. P. PRIOR, M.B. 524

Sobering-up. BRUCE H. BOERES, B.M. 524

Light After Dark. J. F. FILBEE, M.D. 525

Lolly Rash? ALUN LLOYD-JAMES, M.B. 525

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON W.C.1

No. 5250, WEEKLY, PRICE 3/-

Copyright © 1961

REGISTERED AS A NEWSPAPER

FOUR WELL PROVEN WRIGHT-FLEMING VACCINES

are now available, for your convenience,
under short, descriptive, easy-to-remember trade marks:—

POLLACCINE
pollen vaccine for hay fever desensitisation

FLUGEN
influenza virus vaccine

BRL

CATRAGEN
catarrh vaccine

TRIGEN
diphtheria-tetanus-pertussis vaccine (DTP/Vac)
TRIPLE ANTIGEN

Like all other vaccines prepared by the WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, Trigen, Flugen, Catragen and Pollaccine are distributed solely by

BEECHAM RESEARCH LABORATORIES LIMITED
BRENTFORD · ENGLAND · ISLeworth 4111

Full particulars available on request.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 19 1961

DIURETICS AND THE EYE*

BY

DOROTHY ADAMS CAMPBELL, M.B., F.R.C.S.

Research Department, Birmingham and Midland Eye Hospital

This lecture is given annually to honour the memory of Richard Middlemore, who was appointed surgeon to this hospital in 1828. In his day he was obviously a keen observer and a competent ophthalmic surgeon. In 1835 he published his *Treatise on the Diseases of the Eye*, which is a résumé of lectures he gave to members of the medical profession. That he was particularly aware of the importance of relating ocular disorders to the state of the body as a whole is shown by the following quotation from his first lecture:

"I do not profess to give an elaborate account of the progress of ophthalmic knowledge, but may briefly mention, in these preliminary observations, that, in former times, the treatment of diseases of the eye was in a great measure confined to *Oculists*,—to a class of persons assuming that name,—who very frequently acquired, with great notoriety, considerable wealth and importance. You will not fail to remark that these persons, as their conduct and writings evinced, were characterized by extreme assurance and extraordinary ignorance, and that their treatment of ophthalmic disease consisted almost entirely in the rude and unscientific application of disgusting local remedies. If, however, by the term *Oculist* is meant a person competent to treat the various maladies of the human eye, without any, or only a very slight acquaintance with general anatomy, pathology, and therapeutics, we may confidently assert that there is no such individual in existence; for he only can be considered adequate to the treatment of disease, in whatever part it may be situated, who is conversant with the natural structure of parts, with the laws which regulate the healthy functions, and with the derangements and alterations produced by the encroachments of disease,—with the sympathies, the influences and the connexions subsisting between every part of the animated machine. If, however, in defiance of common sense, you do attempt to disconnect the study of diseases of the eye from the cultivation of the other branches of your profession—if, in short, you isolate, as it were, the pathology of the eye, and affect to study its diseases for the purpose of becoming mere *oculists*, you must inevitably fail in your attempts to obtain even an approach to a sound and perfect acquaintance with them. Such, at least, are the views I have formerly expressed and always entertained, and they are decisively sanctioned by my learned friend Mr. Lawrence, in his recently published work. I shall take the liberty of reading to you his opinion upon the subject. Referring to the human body, he says, 'in such a system, then, of intricate connexion and mutual influence, each part will be best understood by him who has the clearest notions of the general economy.'"

The principles expressed by Richard Middlemore have been upheld by those who have followed him, and this Memorial Lecture is designed for general practitioners as well as for ophthalmologists. It therefore seemed appropriate for me to choose a subject relating the eye to the reactions of the body as a whole and to base my observations on research work conducted in this hospital. Some of the work is familiar to you already, but on this occasion I propose to review it from the point of view of the "nature of the systemic action of certain diuretics as compared with others, and of the concurrent effect of each upon the eye."

*The Middlemore Lecture delivered at the Birmingham and Midland Eye Hospital on September 23, 1960.

Diuretic Action of Urea and of Water in Migraine

My interest in the action of diuretics began during the war, when there was a marked increase in cases of migraine, many of which found their way to my ophthalmic department.

At about that time Dr. J. A. Brown (1943), a general practitioner of this city, but who was then the R.M.O. at the General Hospital, had reported that a patient who had suffered from severe migrainous headaches for many years, and who had been admitted to hospital for investigation with a view to operation for cerebral decompression, suddenly became free from headache on the morning after a urea concentration test. This patient escaped operation and was later discharged on regular doses of urea and remained free from symptoms for nine years, so long as he continued to take urea.

Urea is, of course, a relatively harmless diuretic, and in view of this case, and of the fact that the natural termination of an attack of migraine is a spontaneous diuresis (Fig. 1), I treated the patients as a temporary measure with regular oral doses of urea. Many of them responded well, especially those in whom oedema developed before an attack. Their attacks gradually diminished in frequency and severity, and in many cases ceased entirely.

The opening of the Research Department of this hospital in 1947 provided an opportunity of investigating the nature of the biochemical changes which follow the use of a diuretic in migrainous subjects. My colleagues and I (Campbell, Hay, and Tonks, 1951) explored the effects of water diuresis, and found that, whereas the increase in the volume of urine was the same in normal and in migrainous subjects, the latter excreted an unusually large amount of sodium and chloride (see Fig. 5). Furthermore, they appeared to retain both sodium and water prior to an attack—as shown by the high level of sodium in the blood, and by its low colloid osmotic pressure (Fig. 2). In the natural diuresis which followed an attack there was a large output of sodium (Fig. 1). From this we concluded that the beneficial effect of a diuretic was probably due to the fact that it prevented this accumulation of sodium and water.

Action of Diuretics in Glaucoma

During the course of this work Dr. Hay (1952) collected some interesting family histories in which either glaucoma or migraine occurred in individual

members of the same family, and this led us to investigate the effects of diuresis in glaucomatous subjects also.

We again used the water-drinking test, which in this instance was of particular significance in relation to the eye, since it is often used as a diagnostic test for glaucoma. It was introduced by Leydhecker (1950), and we confirmed his observations that after imbibition of 1 litre of water the intraocular pressure in normal subjects was affected by only 2–3 mm. Hg, whereas in glaucomatous subjects it often showed a rise of 8 mm. or over (Fig. 4).

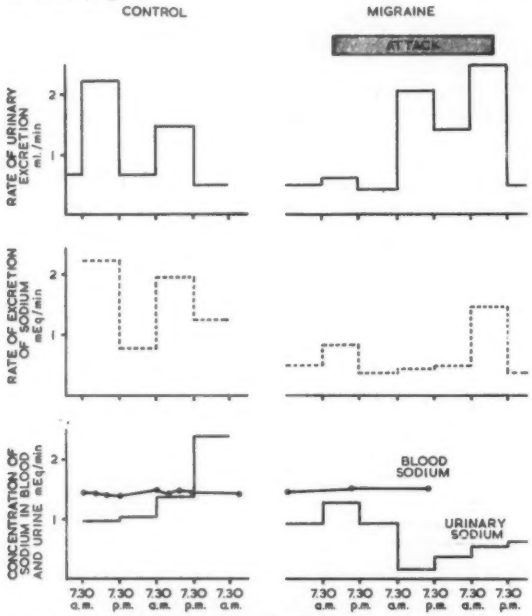

CONTROL
MIGRAINE
ATTACK
RATE OF URINARY EXCRETION ml./min
RATE OF EXCRETION OF SODIUM mEq/min
CONCENTRATION OF SODIUM IN BLOOD AND URINE mEq/min
BLOOD SODIUM
URINARY SODIUM
7.30 a.m. 7.30 p.m. 7.30 a.m. 7.30 p.m. 7.30 a.m.

FIG. 1.—Spontaneous diuresis of sodium and water in migraine (Campbell, 1952, p. 479).

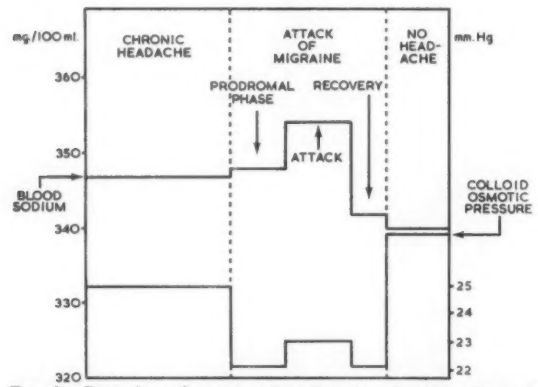


FIG. 2.—Retention of water and sodium in migraine. Normal range: sodium, 320–350 mg./100 ml.; colloid osmotic pressure, 25–30 mm. Hg.

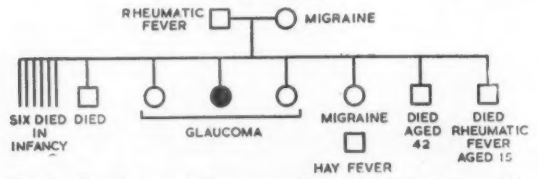


FIG. 3.—Family tree of glaucoma patient (Campbell, 1952, p. 468; after Hay).

We found, moreover, that the ocular response is accompanied by a sharp diuresis of the same type as in the migraine subjects—that is to say that, whereas the volume of urine and rate of excretion is the same as for normal subjects, there is a notable increase in the excretion of sodium (Fig. 5). We found no direct relationship between the levels of intraocular pressure and the concurrent levels of blood sodium. There was, however, evidence of a retention of sodium in glaucomatous patients, as shown by the high average level of blood sodium in the resting state as compared with normal subjects. In these respects there was an obvious similarity between migrainous and glaucomatous subjects, a biochemical finding which was of some interest in view of their likeness in temperament and the familial tendency of these diseases.

We then investigated the action of some of the newer diuretics which had been introduced for the treatment of cardiac oedema, but whose action on intraocular pressure was still unknown, apart from that of acetazolamide ("diamox"), which came into common use at about this time for the relief of glaucoma.

Our observations on human subjects were directed particularly to the action of diuretics in cases of glaucoma with an open angle, for by excluding eyes with a narrow angle—or with obstruction due to secondary

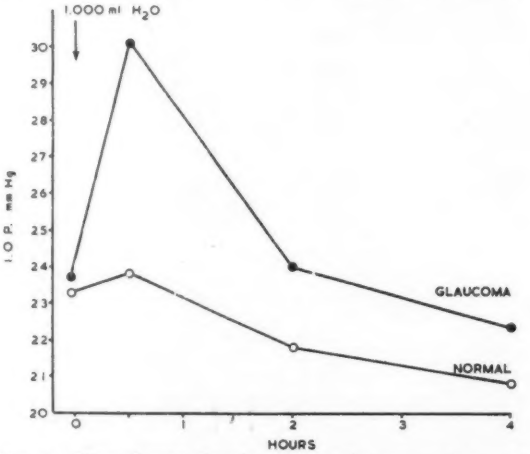


FIG. 4.—Effect of water diuresis on intraocular pressure in normal and glaucomatous subjects.

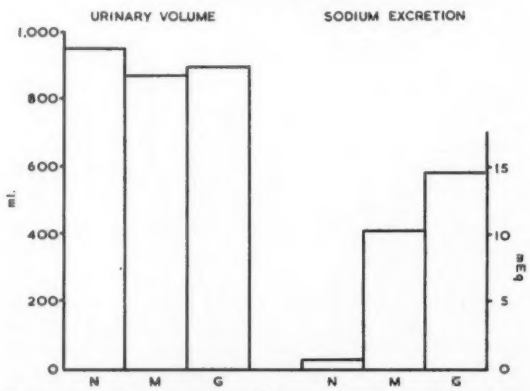


FIG. 5.—Diuresis after water-drinking test (1,000 ml. H_2O), showing increased excretion during four hours after test as compared with four hours before. In normal (N), migraine (M), and glaucoma (G) subjects.

glaucoma, the resultant effect on ocular pressure could be regarded as being unaffected by any pathological obstruction to the outflow of aqueous.

The comparison of the systemic changes with the effect on intraocular pressure was based throughout on a series of careful estimations carried out under standard conditions. The patients were admitted to the research ward, where they co-operated most willingly in the taking of a long series of blood and urine samples and of records of intraocular pressure. They were given a uniform diet (Campbell, Tonks, and Jones, 1956; Campbell, Jones, Renner, and Tonks, 1957; Campbell, Renner, and Tonks, 1958; Campbell, 1960), with a sodium intake of not more than 40–45 mEq in 24 hours. They were also maintained in a state of steady hydration, 140 ml. of water being given at hourly intervals two hours before and three hours after the test dose. No miotics were used, so that the effect of the diuretics on intraocular pressure was not obscured, as has been the case in so much of the work previously recorded by other investigators.

An initial period of observation for the first three days provided an opportunity for observing the diurnal variations during the resting state and allowed the patient to become accustomed to the routine of investigation. Furthermore, we were able to assess the effect of the diuretic over and above the normal diurnal variations during the control period.

Throughout this work we had in mind two considerations: (1) to discover the clinical effect and optimum dosage of those diuretics which reduce intraocular pressure; and (2) to ascertain the nature of the relationship, if any, with the concurrent systemic biochemical changes.

Effect of Diuretics on Intraocular Pressure

Response to Single Doses of Diuretic

According to Pitts (1959) the various types of diuretics can be classified on a functional basis according to their action on the kidney. Those which we selected for investigation are shown in this way in Table I. Their diuretic action depends largely on the amount of sodium excreted, since this ion always carries water with it, and they either increase the filtered load of sodium and chloride ions or antagonize the tubular reabsorption of these ions. Their effect on intraocular pressure is summarized in Table II.

TABLE I.—*Functional Effect of Selected Diuretics (After Pitts, 1959)*

Physiological

1. Water: Impairs reabsorption of sodium by increasing velocity of flow.
2. Urea: Promotes osmotic diuresis by inhibiting tubular reabsorption of sodium and water.

Pharmacological

1. Diuretics which specifically inhibit transport mechanisms for sodium and or chloride ions.
   - (*a*) Meralluride (" mercardan ") (mercurial diuretic + theophylline).
   - (*b*) Chlorothiazide (" saluric "). Chlorthalidone (" hygroton ").
   - (*c*) Aminometradine (" mictine ").
2. Diuretics which interfere with hydrogen for sodium exchange.
   - (*a*) Potassium salts.
   - (*b*) Acetazolamide (" diamox "). Methazolamide (" neptazane ").

TABLE II.—*Effect of Selected Diuretics on Intraocular Pressure*

Acetazolamide .. 250 mg. Methazolamide .. 250 mg. Urea .. .. .. 45 g.	Fall; maximum in	2 hours 3 hours 1 hour
Chlorothiazide .. 1·5 g. Chlorthalidone .. 200 mg. Aminometradine .. 200 mg.	No effect above usual diurnal variation	
Meralluride .. .. 1 ml. intramuscularly	Slight rise in 1–3 hours	
Water .. .. .. 1,000 ml.	Rise; maximum in ½ hour	

If the records taken on the test day are compared with those on the control day the true effect is shown —that is, over and above the usual diurnal variation (Fig. 6).

It is apparent that in the normal therapeutic doses urea and the carbonic anhydrase inhibitors acetazolamide and methazolamide each promote a considerable fall in intraocular pressure. This is also true of their related compounds ethoxolamide (" cardrase ") and dichlorphenamide (" daranide "). The effect of chlorothiazide and chlorthalidone is negligible, as is also that of aminometradine, while meralluride causes a slight rise in pressure of 2–3 mm. Hg only in the course of three hours.

In the case of acetazolamide (Campbell *et al.*, 1956) and the related compound methazolamide (Campbell,

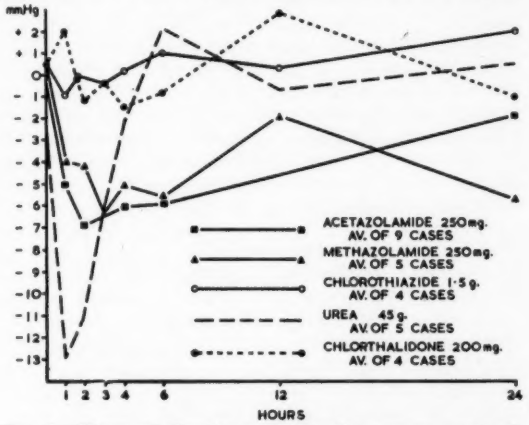


FIG. 6.—Effects of diuretics on intraocular pressure, each administered at 10 a.m. Pressure readings corrected for diurnal variation.

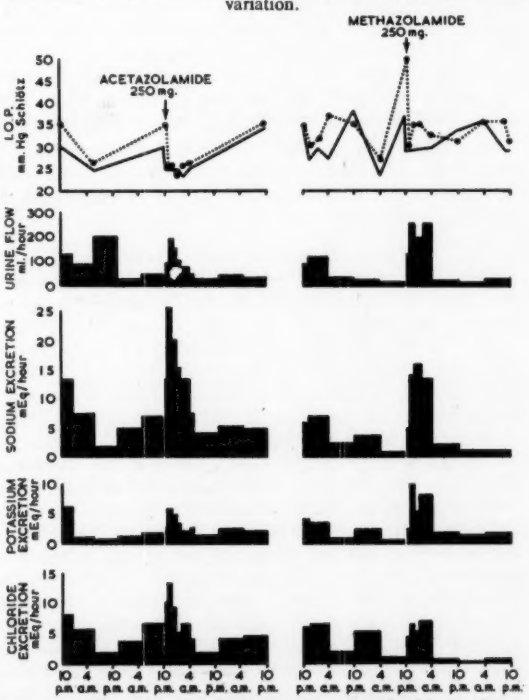


FIG. 7.—Effect of acetazolamide and methazolamide on intraocular pressure and urinary output.

1960) we have been able to show that there is a close time-relationship between the effect on urinary excretion and the changes in intraocular pressure in glaucomatous patients. The period of hypotensive action coincides with the period of diuresis, and of the increased excretion of salts, particularly of sodium.

The response to a single dose of 250 mg. of either acetazolamide or methazolamide is almost identical (Fig. 7) in causing a maximum fall in intraocular pressure in four hours which may last for 24 hours. In practice, the time of choice for administration is just before the peak of diurnal variation.

The minimal effective dose of urea proved to be 45 mg. (30 mg. having no effect). It is unpalatable in any kind of vehicle, and is apt to cause nausea or vomiting. It also gives rise to an occipital headache spreading into the cervical region, the onset of which coincides with the fall in intraocular pressure and disappears when the latter rises again to normal. The administration of 25 mg. of promethazine theoclate two and a half hours prior to the urea will obviate the gastric symptoms but not the headache, while having no effect on the intraocular pressure. The immediate effect of urea is much more pronounced than that of either methazolamide or acetazolamide, being at a maximum within an hour and lasting for only three hours. This confirms the observations of Galin, Aizawa, and McLean (1959a, 1959b), who used a similar dose of lyophilized ammonia-free urea (1.5 g./kg.) dissolved in iced cherry syrup, which caused a marked fall in intraocular pressure in two and a half to three hours.

The development of headache actually precludes its use in large doses, but there is a possibility, which we have not yet explored, that urea might prove efficacious if given in divided doses throughout the day.

In comparison, intravenous urea (Javid, 1958; Galin *et al.*, 1959a, 1959b), when given in a dose of 1 g./kg. in 30% solution in 10% invert sugar, has a maximum effect on the eye in 30 to 45 minutes, and is potentially a useful method for the pre-operative reduction of intraocular pressure. (Cf. its use for the reduction of intracranial pressure (Stubbs and Pennybacker, 1960).)

So far as the medical treatment of glaucoma is concerned, it is apparent that acetazolamide must still be the diuretic of choice, since urea is so unpalatable, and methazolamide is not yet available in this country.

Response to Repeated Doses of Diuretic

Our experience has shown that in repeated daily doses the effect of acetazolamide on the intraocular pressure steadily diminishes (Fig. 8). This is associated with a decline in the excretion of bicarbonate, of sodium, and to a less extent of potassium (Campbell *et al.*, 1957). The loss of bicarbonate from the body is counterbalanced by the retention of chloride, and as a result a state of acidosis develops which may last as long as 48 hours after a single dose, and the eye becomes resistant. Furthermore, after prolonged dosage there may be a serious degree of hypopotassaemia; but this deficiency can be overcome, and the effect of acetazolamide can be restored by giving additional doses of a potassium salt—for example, potassium bicarbonate in doses of 1 g. three times a day. In the case shown in Fig. 9, for instance, the state of glaucoma in the left eye was resistant to the combined action of acetazolamide and miotics, but responded well to acetazolamide and potassium bicarbonate, each of which has a similar action on the kidney.

In practice, in mild cases, such as the elderly patient with chronic glaucoma for whom surgical measures are undesirable, it is often sufficient to give a dose of acetazolamide twice a week, thus allowing the body time to recover from acidosis in the intervals. The blood potassium can often be maintained effectively from naturally rich sources of diet—for example, orange juice, etc. In cases in which the intraocular pressure rises in the evening miotics can also be used with advantage, thus avoiding the serious diminution in vision which is caused in the daytime by miosis in patients who have the added complication of senile cataract.

Long-term Therapy

Long-term therapy with acetazolamide (or methazolamide) should not be embarked upon lightly. In the

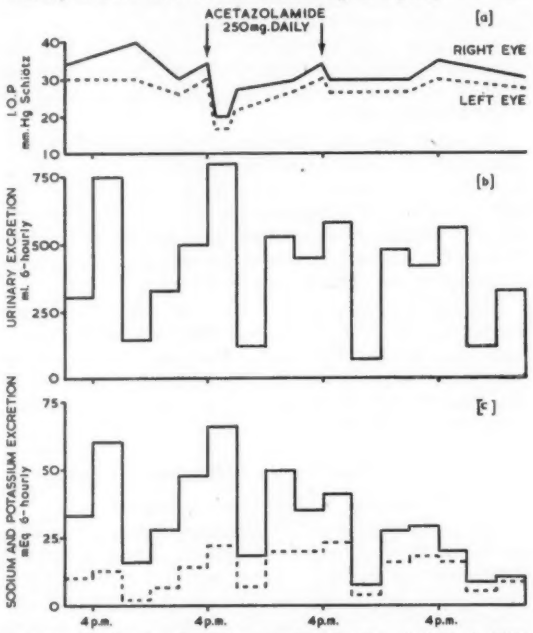


FIG. 8.—Decline in effect of acetazolamide (Campbell *et al.*, 1957, p. 754).

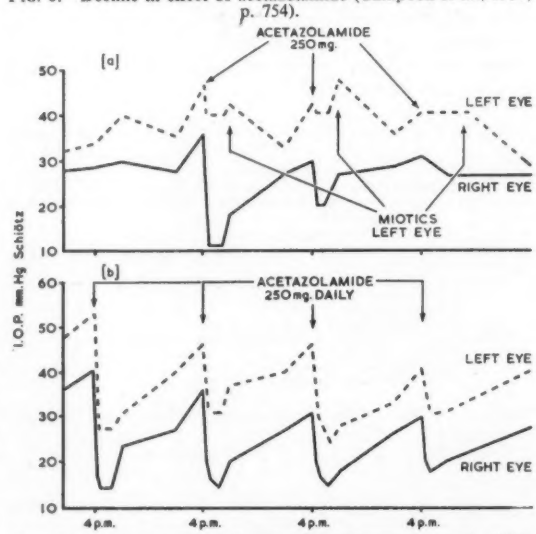


FIG. 9.—Adjuvant effect of potassium (Campbell *et al.*, 1957, p. 751).

first place, it is wise to exclude the presence of renal disease and to ascertain whether a patient is being treated with other diuretics for another cause. Particular care should be taken in giving acetazolamide to diabetics.

So far as the development of hypopotassaemia is concerned, it is our practice in the glaucoma clinic of this hospital to estimate the blood electrolytes at intervals of two to three months in all patients who are on long-term therapy. They are readmitted for control of the dosage if the electrolyte balance is not satisfactory.

A query has also been raised whether long-term administration of acetazolamide might cause osteoporosis by an excessive loss of calcium. We could find no biochemical evidence of this in the level of the blood calcium or any evidence of osteoporosis in a series of *x*-ray films on patients on long-term therapy. In addition, over 100 alkaline phosphatase tests carried out on the blood were all normal, thus verifying the absence of bone or liver damage.

Cases of renal colic have been reported (Becker, 1955; Barraquer and Escribano, 1957; Wynne Davies, 1959) some of which were found to have renal calculi—which may have been pre-existent. All of them had had most intensive therapy, receiving in one instance as much as 250 mg. four times daily; in another (Glushien and Fisher, 1956), crystals resembling acetazolamide were actually found in the renal tubules. There is no doubt that the persistent acidosis which the drug provokes would favour the deposition of crystals, but this can be prevented if potassium bicarbonate is always given in long-term therapy and acetazolamide is limited to a single daily dose. This helps to maintain a normal electrolyte balance and to prevent the progressive loss of potassium to which I have already referred.

With these precautions acetazolamide can be continued for several years.

Methazolamide.—In America, methazolamide has been used successfully (Becker, 1957) in cases which do not respond to acetazolamide. It is also particularly suitable for long-term therapy, since, according to our observations (Campbell, 1960), its effect does not appear to diminish (Fig. 10) and a daily dose of 125 mg. is quite adequate (Fig. 11). It is noteworthy that a second dose given at night after an interval of 12 hours has little additional effect on intraocular pressure, but increases the output of potassium and sodium (Fig. 11).

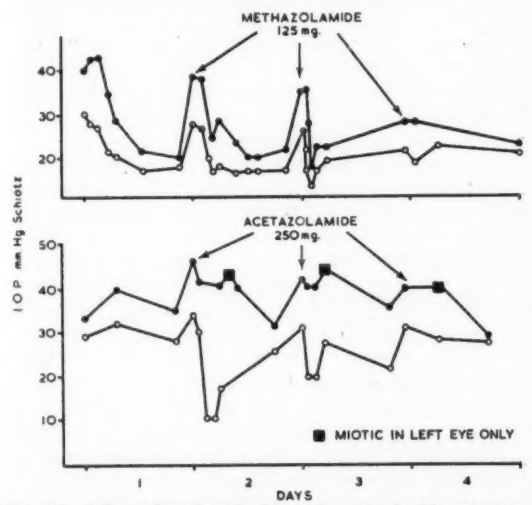


FIG. 10.—Effect of methazolamide and acetazolamide on intraocular pressure (Campbell, 1960, p. 426).

Relationship Between Systemic Effects of Diuretics and Concurrent Variations in Intraocular Pressure

From experimental work on animals it was at first thought that acetazolamide reduced the intraocular pressure by preventing the secretion of aqueous humour, as the result of the inhibition of the formation of the bicarbonate ion within the eye. Langham and Lee (1957) proved, however, that it only brings about a reduction in intraocular pressure when it is administered systemically, and is without effect when introduced locally. Becker (1955) also had shown, in rabbits, that its action on the eye still occurred in nephrectomized animals, which suggests that it is the indirect outcome of a readjustment in the body fluids.

Sir Stewart Duke-Elder (1957), in his Bowman Lecture on the aetiology of simple glaucoma, attributed the fall in intraocular pressure after acetazolamide to a decrease in the base-binding capacity of the blood, and suggested that the decrease in the formation of aqueous humour arises primarily from a disturbance of the osmotic relation between blood and aqueous humour.

Experimental

In order to explore this hypothesis as applied to the human subject, we carried out a further series of experiments to compare the systemic effects of several of these diuretics—namely, chlorothiazide, aminometradine, and urea, together with that of the carbonic anhydrase inhibitors acetazolamide and methazolamide. The results given are the average for a group of five patients in each case—except in the case of aminometradine, with which only two patients were tested. Detailed analyses of blood and urine were carried out con-

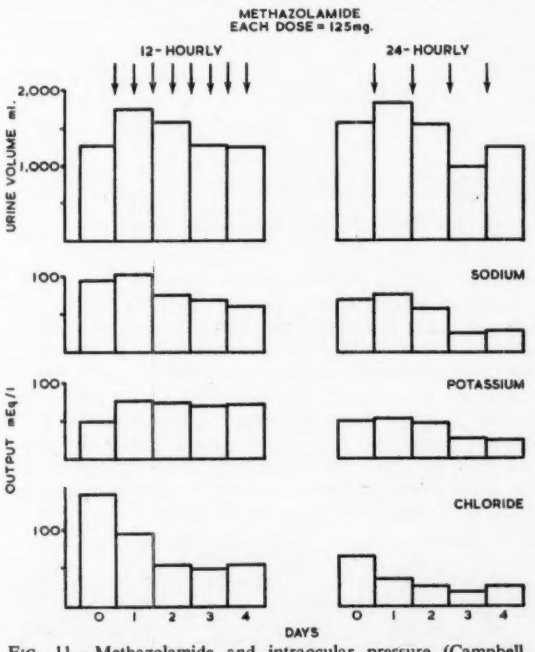


FIG. 11.—Methazolamide and intraocular pressure (Campbell, 1960, p. 427). Day 0=control day. Each daily output is the total for 24 hours.

currently with the records of intraocular pressure, under the standard conditions already described. Except in the case of aminometradine, full analyses were also made on the (pre-dosage) control day. Each diuretic was administered in its normal therapeutic dose.

Urine estimations were confined to volume, *p*H, and sodium, potassium, and chloride excretion. Bicarbonate estimations were omitted owing to the technical difficulty and the undesirable disturbance of the patient, which would have been necessary for the collection of specimens. In the blood we were able to analyse all the constituents, including bicarbonate, as required.

In assessing the relationship between the systemic and intraocular effects the comparison is limited to the period of four to six hours after the dose—that is, to the period during which the maximum effect on intraocular pressure occurred (Figs. 12 and 13).

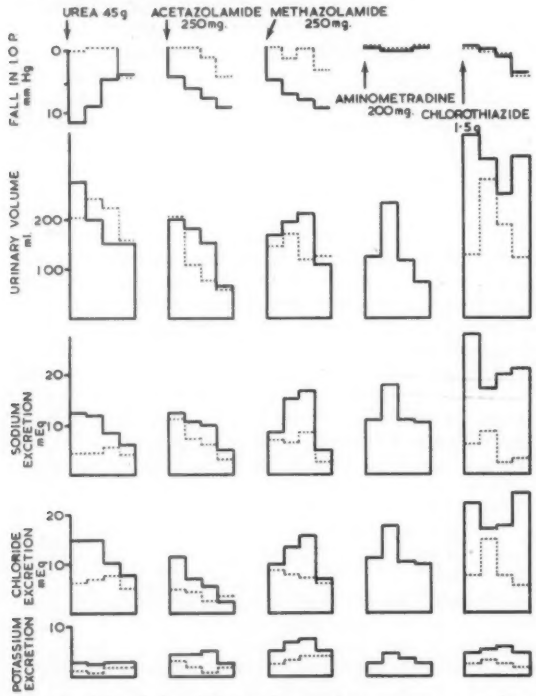


FIG. 12.—Diuresis in relation to intraocular pressure. ——: Test day. - - - -: Control day.

Urinary Output

It can be seen from Fig. 12 that except in the case of urea the fall in intraocular pressure does not run parallel with the volume or rate of urinary output. In comparison, after acetazolamide, methazolamide, and aminometradine the urinary output, although moderate in amount, is accompanied by a sustained fall in intraocular pressure in the case of the first two diuretics and by no change at all after aminometradine. Chlorothiazide, on the other hand, promotes a very large diuresis with virtually no effect on intraocular pressure.

Electrolyte Excretion

Acetazolamide and methazolamide, being carbonic anhydrase inhibitors, cause a considerable disturbance in the electrolyte balance. There is a notable increase in the excretion of sodium (Figs. 7 and 12), which is in excess of chloride and known to be accompanied by a heavy loss of bicarbonate. Both of these diuretics cause a conspicuous fall in intraocular pressure.

Chlorothiazide combines the diuretic properties of a carbonic anhydrase inhibitor and mercurial diuretic—that is, it blocks the reabsorption of sodium and chloride with little effect on the bicarbonate excretion. Sodium and chloride were excreted in equimolar amounts. This also occurred after aminometradine, and neither of these diuretics had any significant effect on intraocular pressure (Fig. 12).

Urea differs from the other diuretics in promoting an osmotic diuresis that is diminished by the extent to which urea itself is reabsorbed by the renal tubules. We found that during the first four hours only one-sixth of the dose was excreted, which meant that the concentration of urea in the blood remained very high. It caused a moderate excretion of sodium and chloride, with a slight preponderance of the latter, and the urine remained acid. The electrolyte pattern of the urine was in fact similar to that after chlorothiazide and aminometradine, which suggests that the disturbance in the electrolytes was not related to the hypotensive effect of urea on the eye.

Changes in Constituents of the Plasma

In considering the changes in the blood it is evident that there is a rapid and continuous adjustment to the excretion of water and of electrolytes on the one hand, and to the demand of the tissues for these substances on the other.

On the whole the pattern of the electrolytes in the blood was a reflection of the urinary excretion. Each of the four diuretics—acetazolamide, methazolamide, chlorothiazide, and urea—caused a fall both of sodium and of bicarbonate, which was, however, significant only in the case of the carbonic anhydrase inhibitors, when it was compensated by a rise in chloride.

In comparing the relative concentrations of sodium and chloride, no significant alteration was found after chlorothiazide and urea—as compared with that occurring at the same time on the control day. It is noteworthy that sodium and chloride were excreted in equivalent amounts after each of these diuretics.

After acetazolamide and methazolamide, however, there was a marked disturbance in the proportional concentrations of sodium and chloride in the blood during the period of fall in intraocular pressure as compared with the control day; this was mainly due to the rise in chloride.

Osmolarity

The combined effect of the disturbances of the principal ions of sodium, potassium, chloride, and the bicarbonate radical is shown in Fig. 13 in terms of

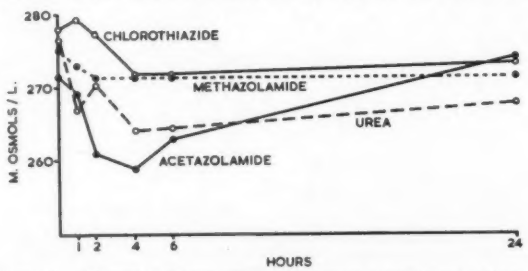


FIG. 13.—Change in serum osmolarity due to electrolytes. (Na^+, K^+, Cl^+, and HCO_3^- on test day).

osmolarity. It falls to a varying degree after each diuretic, but when compared with the same period on the control day the fall is significant only after acetazolamide and methazolamide.

A comparison of the total protein-free osmolarity of the blood, as calculated from its total electrolyte and urea content, also showed a fall after acetazolamide (Fig. 14). But after urea there is a very marked rise,

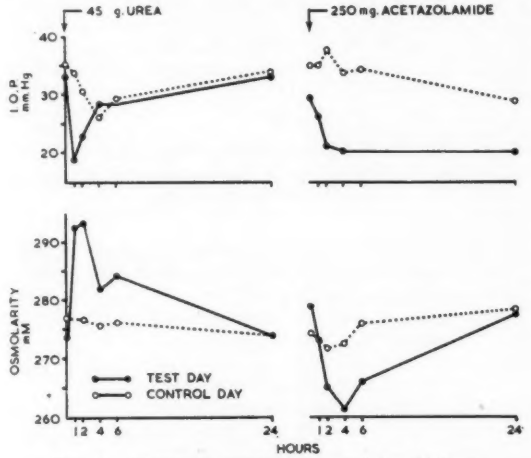


FIG. 14.—Change in protein-free osmolarity of blood.

which is referable to the high concentration of urea. This was also found by Galin *et al.* (1959a, 1959b), who observed that after urea the maximum increase in blood isomolarity (as measured by the depression in the freezing-point) coincides with the maximum fall in intraocular pressure. It does not explain why in our cases the intraocular pressure rises again while the osmolarity is still high, and further investigation on this point is obviously required.

Discussion

In comparing our present knowledge with that of Richard Middlemore it is interesting to recall that before the invention of the ophthalmoscope he and his contemporaries found it difficult to distinguish clinically between cataract and glaucoma until Sir William Mackenzie (1830) observed that the intraocular pressure was raised in the latter condition. Richard Middlemore found by dissection of glaucomatous eyes that the fluidity of the vitreous was increased, and on this evidence treated acute glaucoma by a mercury diuretic in the form of blue pill. This was administered in doses of 5 gr. (0.32 g.) night and morning until "all sense of fullness and uneasiness of the eyeball had disappeared." If the gums were much affected before that beneficial change had occurred he resorted to aperients or to surgical treatment by paracentesis.

Some years later Priestley Smith (1879), also a surgeon of this hospital, suggested that glaucoma was due to faulty drainage at the angle of the anterior chamber rather than to hydrops of the vitreous.

The fundamental observations of these two surgeons have stood the test of time, and many others have been made since their day; but the problem of glaucoma still remains unsolved. Admittedly there are factors of a vascular, neurogenic, or hormonal nature which also influence intraocular pressure, but there is an increasing amount of evidence that an exchange of water and ions is continually taking place between the eye and the plasma, and that intraocular pressure depends on this balance rather than upon any active selection in the secretion of aqueous humour.

It is obvious that the healthy eye with a free outflow can adjust itself readily to changes in the plasma engendered by water intake or by water or electrolyte output. As a result, for instance, it does not share in any state of generalized oedema of the body by developing an increased intraocular pressure, although it may occasionally develop oedema of the tissues of the retina. A sudden dilution of the plasma, as in the water-drinking test, again has little effect on the healthy eye, but causes a rise in intraocular pressure in the glaucomatous eye, in which the outflow mechanism is impaired. In the same way the hypotensive action of diuretics such as methazolamide and acetazolamide is much more pronounced in the glaucomatous eye than in the normal eye, which in itself suggests that diuretics exert their effect on the inflow. There is ample evidence to show, for instance, that neither water (Leydhecker, 1950) nor acetazolamide (Langham, 1955) affects the rate of outflow; indeed, according to Davson (1956) this is impossible on a physiological basis because the area of contact in the region of the angle of the anterior chamber is so small that it could not influence the process of diffusion between plasma and intraocular fluid at this site.

While agreeing with Langham and Lee (1957), that the essential difference in the final equilibrium between the plasma and the eye in normal and glaucomatous subjects is determined by the different properties of the hypertensive eye, this cannot be wholly so. There is evidence, as already stated, that the glaucomatous subject retains sodium—which is excreted in abnormally large amounts after water diuresis (Campbell *et al.*, 1951)—and exhibits a marked lability of his resting blood sodium (Campbell, 1952). Moreover, in the variation of the electrolyte balance in the blood after acetazolamide the change in the sodium content is far greater than that of any other ion (Campbell *et al.*, 1958) in relation to the changes in intraocular pressure. The importance of this systemic factor is supported by the work of Cole (1960), who found that in rabbits, when the effect of outflow is removed by blocking the anterior angle of the eye, the rate of active transfer of sodium appears to determine the rate of entry of water into the eye. On this conception it is possible that a reduction in the rate of sodium influx, which may depend in turn on the concentration of sodium in the plasma, will cause a fall in intraocular pressure in the glaucomatous eye but will have no effect on the healthy eye. In the human subject this response can be detected only when the underlying changes in the blood occur rapidly—as, for instance, after a diuretic.

The biochemical investigation of the action of diuretics in the human subject has provided a sounder basis for their therapeutic use in glaucoma and some additional evidence on their mode of action upon the eye.

The changes in intraocular pressure appear to be closely associated either with a disturbance in the acid-base balance of the blood, in which sodium plays an important part, or with alterations in osmolarity. To what extent these are interrelated is as yet unknown. It is a recognized principle that in the ordinary processes of exchange of fluid throughout the body no water can

pass through a cell membrane without its dissolved salt (O'Donovan, 1960). This probably applies also to the entry of fluid into the eye. There is also good evidence that the ciliary body maintains an active transport of sodium (Cole, 1960), which must be of primary importance in determining the volume of intraocular fluid—that is, the intraocular pressure throughout the day.

In conclusion, I would like to record my appreciation of the honour of being invited to give this Lecture—and of the facilities provided by the Birmingham and Midland Eye Hospital which have made this research work possible.

I am indebted to the editors and publishers of the *Transactions of the Ophthalmological Society of the United Kingdom* and of the *British Journal of Ophthalmology*, respectively, for permission to reproduce Figs. 1 and 3, and 7 to 11.

REFERENCES

Barraquer, J., and Escribano, J. (1957). *Rev. clin. esp.*, **64**, 310.
Becker, B. (1955). *Amer. J. Ophthal.*, **39**, No. 2, Suppl., p. 177.
—— (1957). *Arch. Ophthal. (Chicago)*, **58**, 862.
Brown, J. A. (1943). *Brit. med. J.*, **2**, 201.
Campbell, D. A. (1952). *Trans. ophthal. Soc. U.K.*, **72**, 457.
—— (1960). *Brit. J. Ophthal.*, **44**, 415.
—— Hay, K. M., and Tonks, E. L. (1951). *Brit. med. J.*, **2**, 1424.
—— Jones, M., Renner, N. E. A., and Tonks, E. L. (1957). *Brit. J. Ophthal.*, **41**, 746.
—— Renner, N. E. A., and Tonks, E. L. (1958). Ibid., **42**, 732.
—— Tonks, E. L., and Jones, M. (1956). Ibid., **40**, 283.
Cole, D. F. (1960). Ibid., **44**, 225.
Davies, D. W. (1959). *Brit. med. J.*, **1**, 214.
Davson, H. (1956). *Physiology of the Ocular and Cerebrospinal Fluids*. Churchill, London.
Duke-Elder, Sir W. S. (1957). *Trans. ophthal. Soc. U.K.*, **77**, 205.
Galin, M. A., Aizawa, F., and McLean, J. M. (1959a). *Arch. Ophthal. (Chicago)*, **62**, 347.
—— —— —— (1959b). Ibid., **62**, 1099.
Glushien, A. S., and Fisher, E. R. (1956). *J. Amer. med. Ass.*, **160**, 204.
Hay, K. M. (1952). *Practitioner*, **168**, 271.
Javid, M. (1958). *Surg. Clin. N. Amer.*, **38**, 907.
Langham, M. E. (1955). *J. Physiol. (Lond.)*, **128**, 78P.
—— and Lee, P. M. (1957). *Brit. J. Ophthal.*, **41**, 65.
Lawrence, W. (1833). *Treatise on the Diseases of the Eye*. London.
Leydhecker, W. (1950). *Brit. J. Ophthal.*, **34**, 457.
Mackenzie, Sir W. (1830). *Treatise on Diseases of the Eye*. Longman, London.
Middlemore, R. (1835). *Treatise on the Diseases of the Eye*. Longman, London.
O'Donovan, D. K. (1960). *J. Irish med. Ass.*, **46**, 64.
Pitts, R. F. (1959). *The Physiological Basis of Diuretic Therapy*. Thomas, Illinois, U.S.A.
Smith, Priestley (1879). *Glaucoma*. Churchill, London.
Stubbs, J., and Pennybacker, J. (1960). *Lancet*, **1**, 1094.

"Drugs cost £10,500 more in 1959–60 and medical and surgical equipment £19,000 more. A good deal of the increase for 1959–60 was deliberate, since whatever spare resources were available towards the end of the year were devoted mainly to clearing requests for such items outstanding from previous years because of lack of funds. The results for the third financial year of the new method of hospital costing confirmed earlier impressions that the Board's hospitals are economical in comparison with other like hospitals. At the Royal Hospital in 1959–60, for instance, it cost £25 10s. 1d. to treat an in-patient for one week, which is the lowest cost of all acute teaching hospitals operating the main costing scheme and compares very favourably with an average cost of £30 14s. 11d. per week for acute teaching hospitals in the provinces and £36 6s. 8d. for those in the London area. It is even slightly lower than the average weekly cost of £25 12s. for all acute non-teaching hospitals in England and Wales. Similarly, the cost of an out-patient attendance at the Royal Hospital in 1959–60 was, at 4s. 9d., lower than at any other acute teaching hospital, and also lower than the average for any non-teaching hospital Region in England and Wales." (*United Sheffield Hospitals Twelfth Report*, 1960.)

A NEW VARIANT OF HUMAN INTERSEX WITH DISCUSSION ON THE DEVELOPMENTAL ASPECTS*

BY

PRABHAKER N. SHAH, M.D., F.C.P.S.(Vet.)

S. N. NAIK, B.Sc., M.Sc.

D. K. MAHAJAN, M.Sc.

M. J. DAVE, M.Sc.

AND

J. C. PAYMASTER, F.R.C.S.Ed.

Indian Cancer Research Centre and Tata Memorial Hospital, Parel, Bombay 12, India

The recent chromosome studies on the various intersex states in man suggest that the Y chromosome is strongly male-determining (Jacobs and Strong, 1959; Ford *et al.*, 1959). There is, however, some evidence to suggest that the presence of the Y chromosome is not sufficient to ensure normal development of male gonads and genitalia. In testicular feminization (Jacobs *et al.*, 1959; Grumbach, 1960) and in "pure" gonadal dysgenesis (Harnden and Stewart, 1959) a nearly normal female phenotype develops in the presence of a Y chromosome. Moreover, the development of testicular tissue, and masculinization, in the absence of a Y chromosome in some cases of true hermaphroditism (Harnden and Armstrong, 1959; Hungerford *et al.*, 1959; Ferguson-Smith *et al.*, 1960; Marques de Assis *et al.*, 1960; Shah *et al.*, 1961), suggests that other factors play an important part in influencing the course of sex development. This hypothesis is strongly supported by the present case, in which bilateral testes were found in a patient with apparently an XX sex-chromosome constitution. This patient, but for the cytological studies, would undoubtedly have been classified as a male pseudo-hermaphrodite. We feel that the detailed clinical, endocrinological, and cytological studies on this case provide valuable new information on the spectrum of intersexuality in man.

Case History

The patient was referred to the endocrine clinic at this institution on June 30, 1959, when he was 20 years of age, with ambiguous external genitalia. According to his father, the patient was a full-term spontaneously delivered baby. For the first two weeks after birth the patient's grandmother, however, doubted the correctness of the assignment of sex in view of the size of the phallus, and therefore a doctor was consulted. The family physician confirmed the male sex of the patient and thereafter he was reared as a boy. The father was advised to have the child operated on for hypospadias when he reached the age of 10 years. It was when he was presented for this operation in June, 1959, that he came to our notice.

The father was 35 and the mother 19 years old when the patient was born. The mother had no illness, nor was she given any hormone treatment during the first trimester of pregnancy. Inquiry into the history of the sibs of the father and mother and their children revealed nothing pertinent. The patient is the oldest in a sibship of nine (five males and four females). He has had no serious illness

*Based on the paper presented at the First International Congress of Endocrinology, Copenhagen, 1960.

except cerebral malaria at the age of 2 years and typhoid at the age of 3 years. On the whole he has enjoyed good health, though his physical growth and mental development have always been below normal. His I.Q. is less than 50.

Physical Examination.—At the time of admission the patient was a slightly built, poorly nourished individual with a pigeon-shaped chest. He had no facial or axillary hair. The suprapubic hair was sparse and of feminine distribution (Fig. 1). In the left inguinal canal a reducible round mass 3 cm. in diameter was seen to bulge out (Fig. 2 A). His voice was slightly broken. He weighed 75 lb. (34 kg.) and measured 60 in. (152.5 cm.) in height. He had eunuchoid skeletal proportions; the span was 64 in. (162.5 cm.); pubic symphysis to vertex measured 28 in. (71 cm.), and the sole to pubic symphysis 32 in. (81 cm.). Blood-pressure was 108/70 mm. Hg.

The external genitalia were hermaphroditic in appearance. The phallus was 4.5 cm. in length and 6.5 cm. in girth. There were two skin folds with scrotal rugae and pigmentation, but no gonads could be palpated in these. Separation of these folds revealed a vestibulum in which separate urethral and vaginal openings were present (Fig. 2 B). The vaginal canal measured 7.5 cm. in length. On rectal examination no midline structure—for example, prostate or uterus—was palpable. The rest of the clinical examination revealed nothing of note.

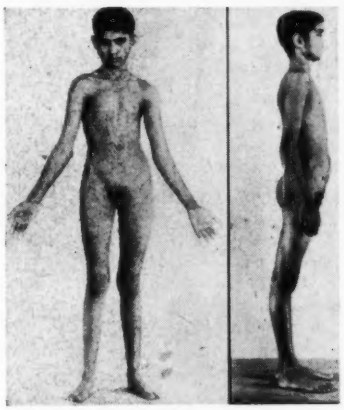


FIG. 1

Laboratory Findings.—The routine urine and blood analyses (including the haemoglobin pattern) showed no unusual feature.

Fluoroscopic examination of the chest disclosed no abnormality. *X*-ray photographs of the limbs revealed no structural abnormality, but the bone age was 14 years. The skull was normal. Radio-opaque material was injected into the vagina under pressure. Fig. 3 shows an *x*-ray photograph of the pelvis in which can be seen a vaginal canal with a thin tract extending into the right pelvic cavity suggesting a fistulous tract—remnant of the Müllerian duct.

The urinary excretion of 17-ketosteroids was 5.5 mg./24 hours (average of three estimations); and the 17-ketogenic steroids excretion was 6.1 mg./24 hours (average of three estimations). The plasma corticosteroids were 20–21 μg./100 ml. of plasma. The urinary gonadotrophins were raised at 100 m.u. per 24 hours.*

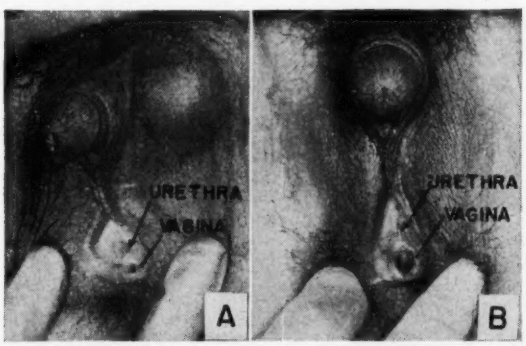


FIG. 2.—Close-up of the external genitalia. A: showing the bulging of a round mass 3 cm. in diameter in the left inguinal region. B: the hermaphroditic appearance of external genitalia.

The findings on laparotomy are shown in Fig. 4. On each side a gonad macroscopically resembling a testis was present. Similarly, structures resembling epididymis and vas deferens

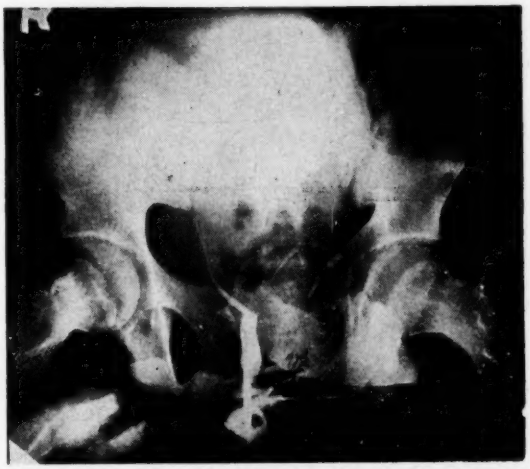


FIG. 3.—*X*-ray photograph of the pelvis after injection of a radio-opaque material, revealing a vaginal canal and a thin tract on the right side representing the remnant of the right Müllerian duct.

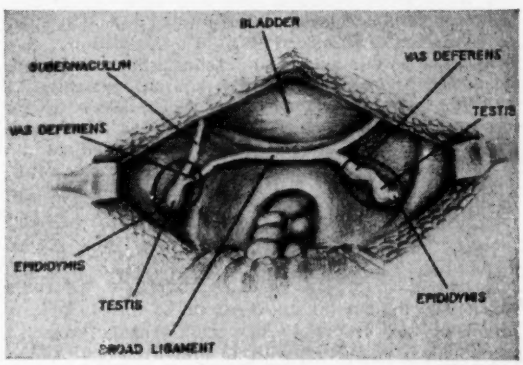


FIG. 4.—Artist's sketch of the findings seen on exploration of the abdomen.

were present on each side. A broad ligament was present but no uterine mass was seen or palpable. The structures shown in the areas demarcated within the dark circle were removed and subjected to histological examination.

Each gonad measured 2 cm. in length, 1 cm. in breadth, and 0.8 cm. in thickness. Histological examination of the gonad stained with haematoxylin and eosin revealed immature seminiferous tubules lined by a single layer of undifferentiated cells. Fields showing six or seven hyalinized tubules were occasionally seen in some of the sections. The Leydig cells were seen in well-defined large clumps localized near the tubules; these cells have vesicular nuclei with well-defined granular cytoplasm (Fig. 5). Sections of the testis stained with Mallory's connective-tissue stain showed a mild degree of tubular fibrosis, and those stained with Weigert's stain revealed a total absence of elastic fibres in the tubular wall of the testes.

Microscopical examination of sections of the organs resembling epididymis and vas deferens on both sides

*At our laboratory the normal hormonal values in women of active reproductive ages are as follows: urinary 17-ketosteroids, 4–13 mg./24 hours; urinary 17-ketogenic steroids, 4–10 mg./24 hours; plasma corticosteroids, 5–22.5 μg./100 ml. of plasma; urinary gonadotrophins, 6–50 m.u./24 hours.

revealed the typical structure of these tissues (Fig. 6 A and B).

The nuclei of the Leydig cells of the testes and also of cells from the skin, the buccal mucosa, and the vaginal epithelium showed a normal female proportion of sex

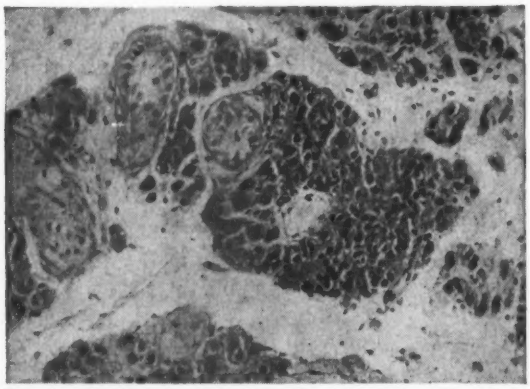


FIG. 5.—Histological section from the right testis. (H. and E. ×140.) The sections from the left gonad were identical in appearance.

chromatin bodies. The sex chromatin bodies were typical and were stained by the modified Feulgen technique (Lillie, 1954).

A skin biopsy specimen was sent from Bombay to Edinburgh, and a culture was established from this tissue by the method of Harnden (1960). The chromosomes were found to be 46 in number and indistinguishable from those of a normal female—that is, they had an apparently XX sex chromosome constitution. The few cells with other than 46 chromosomes are thought to be due to technical errors, and the cell with a count of 47 chromosomes could not have been interpreted as having an XXY sex chromosome constitution (see Table I and Fig. 7). A second biopsy specimen sent later failed to grow.

Discussion

Recent data indicate that Klinefelter's syndrome, which was thought at one time to be an example of complete sex reversal in the chromatin-positive individual, is associated with an abnormal complement of sex chromosomes (Jacobs and Strong, 1959). The only apparent exception is the case reported by Ford *et al.* (1958) to have 46 chromosomes and an XX sex chromosome constitution. This finding was based on

Chromosome Counts From Skin

Chromosome Count					Total Cells	
<45	45	46	47	>48	Counted	Analysed
2	2	26	1	—	31	3

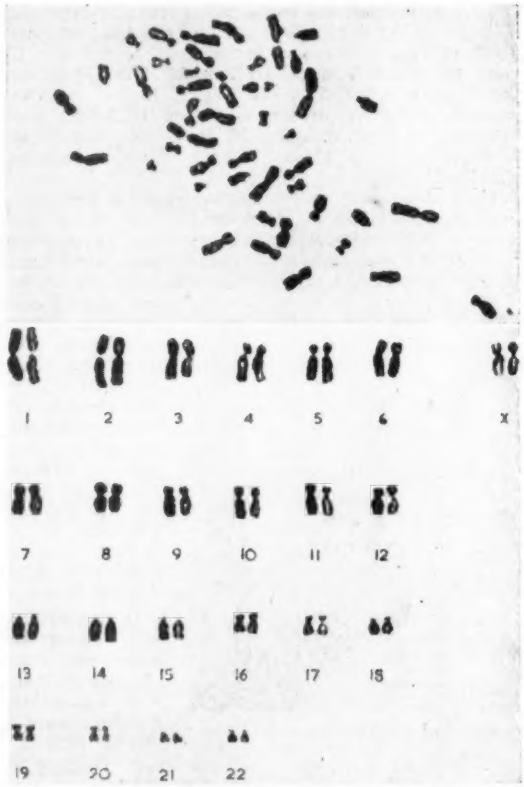


FIG. 7.—Mitotic metaphase of a cell from skin culture. This shows 46 chromosomes and XX constitution.

the examination of only five cells and is therefore not thought to be conclusive. All the other reported cases of chromatin-positive Klinefelter's syndrome appear to have an XXY sex chromosome constitution or are XX/XXY sex chromosome mosaics (Ford *et al.*, 1959).

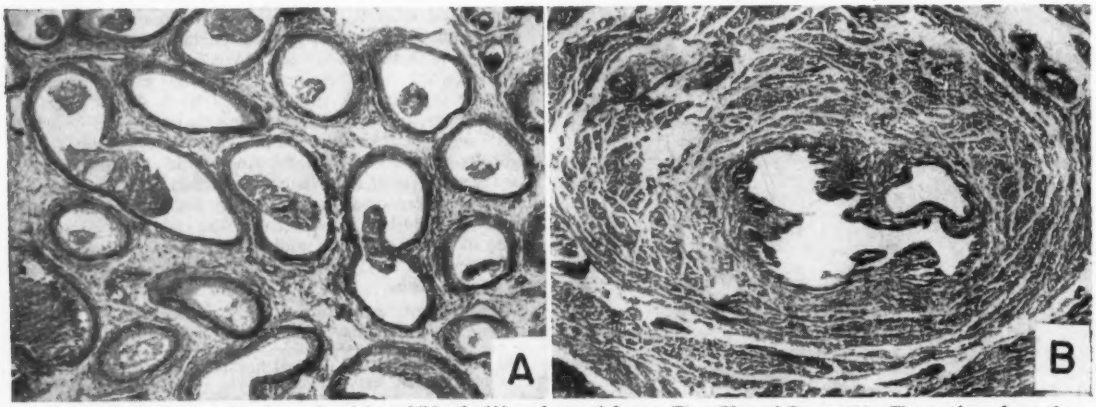


FIG. 6.—Histological section from the right epididymis (A) and vas deferens (B). (H. and E. ×44.) The sections from the similar structures on the left side revealed identical microscopical pictures.

The present patient, therefore, is the first chromatin-positive individual in whom both gonads, on detailed sectioning, proved to be testes and whose sex chromosome constitution is apparently that of a normal female.

This observation in itself suggests that an abnormal complement of chromosomes is not the only mechanism through which abnormal sex development is brought about and that several causal factors may be involved. The fact that all the cases of chromatin-positive true hermaphroditism so far studied have a normal female chromosome constitution also supports this contention (Harnden and Armstrong, 1959; Hungerford *et al.*, 1959; Ferguson-Smith *et al.*, 1960; Marques de Assis *et al.*, 1960; Shah *et al.*, 1961). The finding that there is a female sex chromatin pattern in various tissues of this patient and that the cells of a small skin biopsy specimen have normal female chromosomes does not rule out the possibility that the patient may be an XX/XXY mosaic. This could probably be resolved by examination of the chromosomes from the peripheral blood or bone-marrow, but this is not at present possible.

If by further study we exclude this possibility, two interpretations can be offered for the altered gonadogenesis which would be consistent with the finding of an XX sex chromosome complement. First the sex reversal could have been effected by an autosomal recessive gene mutation such as the one described in *Drosophila* by Sturtevant (1945). An alternative explanation would be that deleterious environmental factors had destroyed the cortex at the time when cortico-medullary competition is occurring. If either of these explanations is correct the present case may be only a partial expression of the phenomenon, and it may be that an individual clinically indistinguishable from a case of chromatin-positive Klinefelter's syndrome may eventually be found to have a normal female chromosome complement.

Whatever the various aetiological factors may be in this particular case, they appear to act either through their influence on the production of foetal testicular morphogenetic secretion or by altering the responsiveness of the tissues to these hormones. The evidence is not at present sufficient to enable one to choose between these two alternatives.

As we pointed out at the beginning, it is wise to think of human intersexuality as a spectrum of cases, or perhaps several such spectra, rather than as a number of clearly defined categories into which individual cases can be neatly fitted. One can postulate a spectrum of individuals with an XX sex chromosome constitution ranging from the normal female on the one hand to the hypothetical Klinefelter's type male with an XX sex chromosome constitution on the other. The present case would fit well into this spectrum. In the normal female only the cortex of the gonad is developed. One half of the spectrum would be composed of individuals with a decreasing amount of cortical development and no medullary development. At the midpoint would be cases of pure gonadal dysgenesis where both cortex and medulla fail to develop (Hoffenberg and Jackson, 1957). The other half of the spectrum would be composed of individuals in whom the cortex failed to develop and in whom there is an increasing amount of medullary development. The case of Greenblatt *et al.* (1956) which is now designated "ovarian dysgenesis with vestigial medullary development," where the cortex fails to develop but where a slight development of the medulla gives a phallic enlargement in an otherwise female phenotype, would be one of the first cases in this progression. The present case where the extensive development of the medulla combined with absence of the cortex leads to a considerable degree of masculinization, would be a link between Greenblatt's case and the hypothetical XX case of Klinefelter's syndrome.

Summary

A case of male pseudohermaphroditism having female sex chromatin pattern in several tissues and normal female chromosome constitution from the skin culture is presented. These findings are discussed in the light of the present knowledge on the developmental aspects of intersexuality.

We are grateful to Dr. V. R. Khanolkar, Director, Indian Cancer Research Centre, for the interest he has shown in this investigation and for his encouragement. We are deeply indebted to Dr. D. G. Harnden, of the Western General Hospital, for carrying out the chromosomal study of this patient. We thank Dr. Warren O. Nelson, Medical Director, Population Council Inc., New York, for reviewing the sections of the testes, epididymis, and vas deferens, and Miss Perin Master for carrying out the I.Q. test of the patient.

REFERENCES

Ferguson-Smith, M. A., Johnston, A. W., and Weinberg, A. N. (1960). *Lancet*, **2**, 126.
Ford, C. E., Jacobs, P. A., and Lajtha, L. G. (1958). *Nature (Lond.)*, **181**, 1565.
—— Polani, P. E., Briggs, J. H., and Bishop, P. M. F. (1959). Ibid., **183**, 1030.
Greenblatt, R. B., Carmona, N., and Higdon, L. (1956). *J. clin. Endocr.*, **16**, 235.
Grumbach, M. M. (1960). In *Clinical Endocrinology* I, edited by E. B. Astwood, p. 407. New York.
Harnden, D. G. (1960). *Brit. J. exp. Path.*, **41**, 31.
—— and Armstrong, C. N. (1959). *Brit. med. J.*, **2**, 1287.
—— and Stewart, J. S. S. (1959). Ibid., **2**, 1285.
Hoffenberg, R., and Jackson, W. P. U. (1957). Ibid., **1**, 1281.
Hungerford, D. A., Donnelly, A. J., Nowell, P. C., and Beck, S. (1959). *Amer. J. hum. Genet.*, **11**, 215.
Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Forrest, H., Roy, J. R., Stewart, J. S. S., and Lennox, B. (1959). *Lancet*, **2**, 591.
—— and Strong, J. A. (1959). *Nature (Lond.)*, **183**, 302.
Lillie, R. D. (1954). *Histopathologic Technic and Practical Histochemistry*, p. 132. Blakiston, New York.
Marques de Assis, L., Epps, D. R., Bottura, C., and Ferrari, I. (1960). *Lancet*, **2**, 129.
Shah, P. N., Mahajan, D. K., and Paymaster, J. C. (1961). Unpublished data.
Sturtevant, A. H. (1945). *Genetics*, **30**, 297.

The *Annual Report of the National Assistance Board 1960* (Cmnd.1410, H.M.S.O.) records a total net expenditure during the year of about £187¼m., of which more than £166m. was for allowances under the National Assistance Act, 1948, and nearly £11m. for non-contributory old age pensions. Weekly national assistance allowances increased in number during the year to 1,857,000. A majority (70%) of the 1,857,000 allowances were being paid to old people. Sick people and others unable to work—for example, women with family ties—accounted for about 23%; less than 7% were unemployed and registering for work. Most recipients —two out of every three—were women; most of these were widows, mainly elderly widows receiving retirement pensions by right of their husbands' national insurance. This year's *Report* also deals specially with three small "problem" groups: men in doubtful health who have a long record of unemployment, men who seem unwilling to work, and the "unsettled" men who frequent reception centres.

CORROSION OF ORTHOPAEDIC IMPLANTS

SMITH-PETERSEN TYPE HIP NAILS

BY

JOHN T. SCALES, M.R.C.S., L.R.C.P.
Senior Lecturer, Department of Biomechanics and Surgical Materials, Institute of Orthopaedics (University of London); Consultant in Orthopaedic Prosthetics, Royal National Orthopaedic Hospital, Stanmore, Middlesex

G. D. WINTER, B.Sc.
Research Assistant, Department of Biomechanics and Surgical Materials, Institute of Orthopaedics (University of London)

AND

H. T. SHIRLEY, B.Sc., A.R.C.S.
Brown-Firth Research Laboratories, Sheffield

[WITH SPECIAL PLATE]

Metal implants are used increasingly in orthopaedic treatment, but from time to time complications occur which seem to be attributable to the implant. A programme of work sponsored by the Nuffield Foundation and the Medical Research Council has been undertaken to investigate the applications of materials in orthopaedic surgery. Part of this work has been concerned with the study of implants removed from patients at the Royal National Orthopaedic Hospital and a number of other hospitals, together with the clinical histories, relevant radiographs, and, where available, histological material.

This report is concerned with the incidence of corrosion of 65 Smith-Petersen type hip nails, with four of which a Pidcock pin was also employed.

The term "implant" is used to describe the complete device, while the individual pieces are called components. Each has been studied in the following way: (1) It has been examined for corrosion and other damage by means of the binocular microscope before and after cleaning in nitric acid (specific gravity, 1.20). (2) The type of alloy has been determined by spectrographic analysis. (3) The hardness has been determined by the Vickers "diamond pyramid" method using a 20-kg. load.

Special techniques were used in the examination of some of the components, including non-destructive flaw testing and sectioning. Gross corrosion and deep pitting corrosion can be easily recognized with the naked eye. Less severe degrees of corrosion are seen as dull patches on the otherwise polished surface of the metal, and under the microscope these have a rough, pitted appearance.

TABLE I.—*Alloys Used for Implants*

Group 1: Low-alloy Steels	Group 2: High-alloy Steels		Group 3: Cobalt–Chromium–Molybdenum Alloys
13% Cr	Chrome–nickel-Austenitic		25/30% Cr, 3/7% Mo, traces of Ni and Mn and Fe, balance Co;
	Martensitic	(*a*)	
	17% Cr, 3% Ni	18% Cr, 8% Ni;	
		(*b*)	
		18% Cr, 8% Ni, 0·6% Ti;	
		(*c*)	
		18% Cr, 8% Ni, 2·5–3·5% Mo	

Co = cobalt
Cr = chromium
Mo = molybdenum
Fe = iron
Mn = manganese
Ni = nickel
Ti = titanium

While they may have a superficial resemblance to mechanical damage caused by abrasion, corroded areas can be easily distinguished after some experience. Every component has been checked for corrosion by each of the authors.

The types of alloy from which the components have been made are shown in Table I.

FINDINGS OF INVESTIGATION

Table II shows the incidence of corrosion of the different types of alloy. The 13% Cr alloy implants had suffered severe corrosion, while the high-alloy steels showed less corrosion. The cobalt–chromium–molybdenum implants were not corroded.

TABLE II.—*Incidence of Corrosion*

Type of Alloy	No. of Components Examined	Incidence of Corrosion
13% Cr	9	9
17% Cr, 2% Ni	2	2
18% Cr, 8% Ni	23*	7 (1†)
18% Cr, 8% Ni, 2·5–3·5% Mo	30*	9 (2‡)
Head of nail: 18% Cr, 8% Ni, 2·5–3·5% Mo Stem of nail: 18% Cr, 8% Ni	1	1
18% Cr, 8% Ni, and up to 0·6% Ti	2	1
64% Co, 30% Cr, 5% Mo	2	0
Total	69	29

* Including two Pidcock pins. † One Pidcock pin corroded. ‡ Two Pidcock pins corroded.

Group 1 Steels

13% Cr Alloy Steel

The dates of insertion of nails made of this alloy are given in Table III. All were inserted after 1940, though it was well known before 1940 that this alloy was not suitable for implants. It is very surprising to find that one nail, A.683, was inserted as recently as May, 1959. No implants made from 13% Cr alloy should now remain in hospital stocks. Since this type of alloy is strongly magnetic, such implants can easily be differentiated from those of austenitic steel.

TABLE III.—*13% Cr Nails*

Implant No.	Date Inserted*	Time in Body
A.46	1946	8 years
A.91	1950	6 ,,
A.175	1944	12 ,,
A.338	1948	8 ,,
A.419	1958	6 weeks
A.460	1940	18 years
A.494	1941	17 ,,
A.606	1942	17 ,,
A.683	1959	14 weeks

* All in United Kingdom.

The nail used in 1958—A.419—was removed after six weeks because the position of the arthrodesis was not satisfactory. There was no extrusion of the nail. The entire surface of the nail was darkly stained and there was a deep corrosion pit in the head (Special Plate, Fig. 1). Nail A.683, inserted in May, 1959, was removed 14 weeks later because of pain associated with penetration of the nail into the acetabulum. There was no extrusion of the nail. The soft tissues over the distal end of the nail were discoloured; there was no evidence of infection, and the wound healed without drainage. Histological examination of tissue from over the head of the nail showed cellular granulation tissue with foreign-body giant cells. There were extensive intracellular and extracellular deposits of iron. The stem of the nail was brightly polished, but there were pits around the rim of the head. In making the nail the head had been fitted to an extension of the stem. The cannula had then been

expanded and the junction of the head with the triflanged portion of the stem soldered. This solder had corroded. The internal surface of the cannula was also corroded along its length. This case illustrates clearly the need to review stocks of implants held by hospitals.

Nail A.91, which had not extruded, was removed after six years because of fibrous ankylosis instead of intended arthrodesis. Rarefaction around the nail seen on the radiograph may have been caused by movement. There was slight pitting corrosion at the junction of the head with the stem on the triflanged surface, and a dark discoloration, with slight pitting of the inner surface of the cannula. Nail A.46, which was severely corroded (Special Plate, Fig. 2), had been inserted in 1946 to arthrodese the hip. The patient complained of discomfort in the hip eight years later, and radiographs showed a clear zone of rarefaction around the nail, which had not extruded but appeared to be loose within its track (Special Plate, Fig. 3). The nail was removed. Another severely corroded nail—A.338—also removed after eight years, had been inserted in 1948 to stabilize a slipped upper femoral epiphysis. Radiographs showed a clear zone of rarefaction around the nail, which had not extruded. A pure growth of *Bacillus coliformis* was obtained on culture of material removed from the cannula of the nail. A nail inserted in 1944—A.175—and removed after 12 years because of acute pain, was severely corroded, and a Pidcock pin of 18/8 alloy had also corroded. Radiographs showed that, following avascular necrosis of the femoral head, the nail, which had not extruded, had penetrated into the acetabulum. There was a zone of rarefaction around the nail. Nail A.494, removed after 17 years following avascular necrosis of the femoral head, was severely corroded. It had penetrated the acetabulum. The nail, which had not extruded, was surrounded by a zone of rarefaction. A Pidcock pin of 18/8 alloy was not corroded.

The most severely corroded nail was A.606. In 1942 a patient aged 47, with osteoarthritis of the left hip, had a Smith-Petersen pin arthrodesis supplemented with an ilio-femoral graft. The arthrodesis was successful, and the patient was free from pain for eight years. Then from 1950 to 1952 she complained of pain in her left hip, knee, and lumbar region. A radiograph taken in 1951 (Special Plate, Fig. 4) showed a corrosion pit midway along the nail with a zone of increased density in relation to the pin at this place. The patient was not seen again until 1959, when because of severe pain she attended hospital. A radiograph showed that the pin had corroded through (Special Plate, Fig. 5). There was no extrusion of the nail. At operation considerable soft-tissue reaction around the head of the nail was found. The distal half of the nail was removed, but the proximal portion could not be extracted. When last seen the patient had a recurrence of the severe pain in the hip. The remaining part of the pin will probably have to be removed at a later date.

Another patient had a Smith-Petersen nail—A.460—inserted in 1940 for fracture of the neck of the left femur. The fracture united satisfactorily, and she was completely well until 1955. From then until 1958 she had gradually increasing pain and developed a slight limp, with limitation of abduction and of internal and external rotation. An antero-posterior radiograph (Special Plate, Fig. 6) showed a zone of rarefaction about the stem of the nail, while a lateral radiograph (Special Plate, Fig. 7) showed corrosion of the distal third of the stem. At operation there was no evidence of infection. A McMurray osteotomy was performed and a four-flanged nail and plate inserted, after which the pain was relieved. The nail, which was black in colour, had corrosion pits all over the outer surface and in the wall of the cannula which communicated in the distal third of the nail. The pain in this case may have been due to developing arthritis or to the corrosion. Nevertheless, it was apparent that the corroding nail was causing a tissue reaction.

Rarefaction of bone adjacent to corroding 13% Cr alloy hip nails usually occurs, but sometimes the reaction is one of sclerosis, as occurred with nail A.606. The same radiographic appearances may be due to infection and movement. Infection was proved in one of these cases, but no swabs were taken from the others. In two cases tissue adjacent to the nail and corresponding to the rarefied areas in the radiographs was examined. It was highly collagenous fibrous tissue with iron-containing deposits (Special Plate, Fig. 8).

Group 2 Steels

17% Cr, 2% Ni Alloy Steel (17/2)

This is a martensitic steel, hardenable by heat treatment like the 13% Cr steels, and of intermediate corrosion resistance between these and the austenitic steels. Two nails were made from this type of steel; both were inserted in Great Britain. The head of one nail—A.699—was a push fit on the distal part of the cannula, which had been swaged to lock the head on the stem. It was used in 1959 to treat a fracture of the femur neck in an elderly female who died one month later. The nail had not extruded. There was slight corrosion on the underside of the head at the interface between the head and the flanges. The head of the other pin—A.720—was screwed on the stem. This pin was used in 1947 to treat a fractured neck of femur in an elderly female. It was removed after 13 years because of pain over the head of the nail, which was extruding. The fracture had united. There were corrosion pits on the head of the nail, which had also cracked. The threaded portion of the nail within the head was corroded and the stem of the nail was generally tarnished. This type of alloy should not be used for the manufacture of implants.

18% Cr, 8% Ni Alloy Steel (18/8)

Twenty-one nails made from 18/8 alloy (20 by the same manufacturer) were examined. One of the nails was constructed of three pieces and three of two pieces; the remainder were of one-piece construction. A quantity of dirt was trapped between the separate pieces. One nail was marked with the code letter which normally denotes 18/8/Mo alloy. With the exception

TABLE IV.—*Reasons for Removal of 18/8 Nails*

Principal Reason for Removal	No. of Nails	No. of Nails Corroded
Extrusion	7	2
Routine	4*	—
Nail penetrated into acetabulum	2	—
Pain without any other obvious complication	2	2
Reduction of fracture not satisfactory	1	—
Arthrodesis not attained	1	—
Broken nail	1	1
Avascular necrosis of femoral head	2	—
Infection	1	1
Total	21	6

* Including nail used for arthrodesis of ankle.

of one nail, the date of insertion of which could not be ascertained, all these nails were inserted after 1947 and had been in the body for periods between 18 days and 7 years. They had been used to treat fractures of the femoral neck (13) and slipped femoral epiphysis (3), and for arthrodesis of the hip (4) and ankle (1). Reasons for removal of the nails are given in Table IV.

Six of the 21 nails were corroded. One nail—A.49—was fractured in two places, the appearance of the fractures being consistent with failure by fatigue, though one fracture had been so severely damaged by rubbing that it was not possible to be certain as to the cause. Microscopical examination of the longitudinal section of the nail up to this fracture showed several small transcrystalline cracks parallel to the fracture. An example is shown in Fig. A. The presence of several cracks such as this would suggest that corrosion fatigue was responsible. There was no obvious sign of corrosion on the outer surface of the nail. The cannula contained a considerable amount of oxide or corrosion products, and from an examination of the etched section it appeared that some intercrystalline corrosion had taken place (Fig. B). There was a quantity of carbide out of solution in the inner surface of the wall of the cannula, which suggested that local carburization had occurred during manufacture (Scales *et al.*, 1959). Carburization is an increase in the carbon content of the steel. In this case it arose from diffusion of carbon from a high-carbon-steel mandrel used in the production of the tube from which the triflanged nail had been machined. Steps have now been taken which should overcome this effect. The other five nails showed slight corrosion in various places on the surface of the stem and the head, at the head–stem junction, and in the cannula. Radiographs showed a zone of rarefaction around five of the 21 nails. Neither the radiological appearances nor the "reason for removal" could be correlated with corrosion of the implant. Five of the nails were accompanied by tissue, but in three cases the tissue could not be definitely related to the implant. Histological sections of the other two specimens which were adjacent to corroded implants showed dense fibrous tissue with collections of particulate material which gave a positive staining reaction for iron.

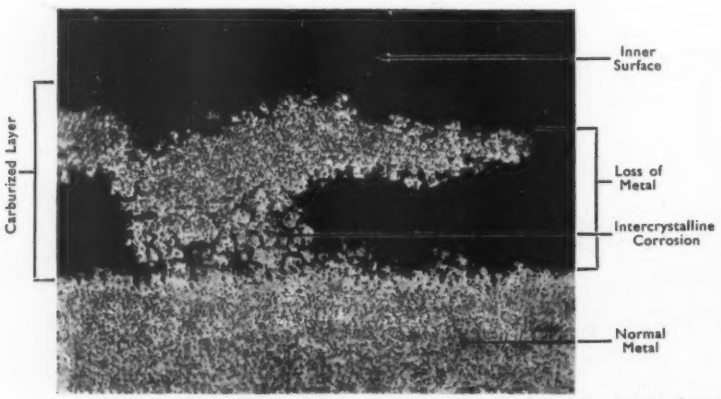
FIG. A.—Nail A.49. Transcrystalline crack parallel to fracture. (×200.)

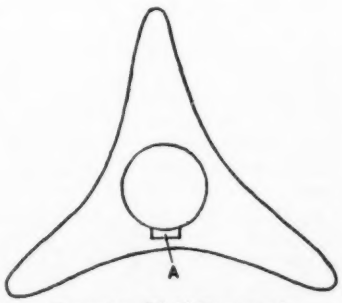
18% Cr, 8% Ni, 0.6% Ti Alloy Steel (18/8/Ti)

Two nails made from 18/8/Ti alloy were examined. One of these was corroded slightly near the pointed end. Both nails had been used for fixation of fractures of the femoral neck in elderly patients and both were removed because of extrusion of the implant, one after three weeks and the other after five months. There were no changes in the bone visible on the radiographs, nor was there clinical evidence of infection. Both nails were marked with the code letter for 18% Cr, 8% Ni alloy steel.

18% Cr, 8% Ni, 2.5/3.5% Mo Alloy Steel (18/8/Mo)

Twenty-eight nails made from 18/8/Mo alloy by three manufacturers were examined. Eight of the nails, proved by spark spectroscopy to be 18/8/Mo alloy, were marked with a code letter which has been used by one manufacturer for plain 18/8 alloy implants. It is important that implants are marked correctly. Two of the nails had been used with Pidcock pins. Four were





Transection of Smith-Petersen nail showing position of section (A)

FIG. B.—Nail A.49. Section (A) through wall of cannula showing intercrystalline corrosion. (×385.)

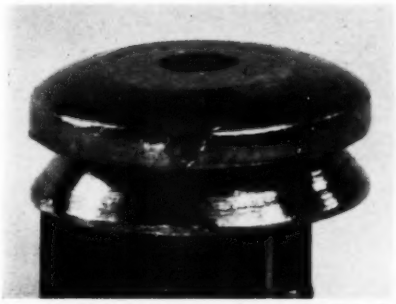


FIG. 1.—Nail A.419. Corrosion pit in head of 13% Cr hip nail removed after six weeks.

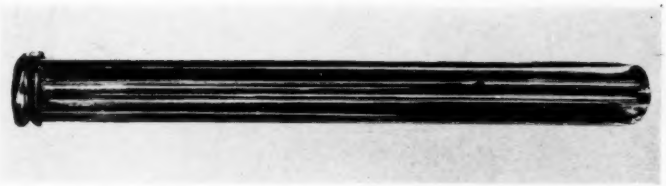


FIG. 2.—Nail A.46. Corroded 13% Cr hip nail removed after eight years

FIG. 3.—Nail A.46. 13% Cr hip nail eight years after operation.

FIG. 4.—Nail A.606 nine years after insertion.

FIG. 5.—Nail A.606 17 years after insertion.

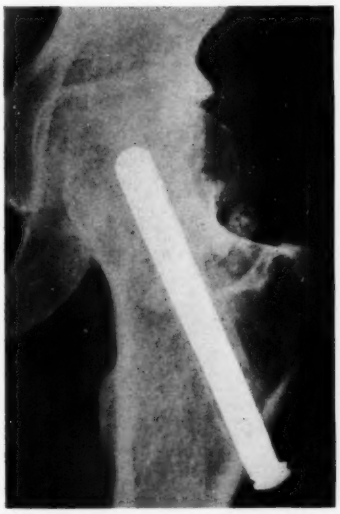


FIG. 6.—Nail A.460. Antero-posterior radiograph of left hip showing zone of reaction around corroded nail. Note that deep corrosion pits are scarcely visible in this view.

FIG. 7.—Nail A.460. Lateral radiograph of left hip. Note corrosion pits in distal third of nail and zone of reaction in bone.

FIG. 8.—Nail A.46. Tissue from around 13% Cr nail after eight years.

J. R. BILLINGHURST *ET AL.*: CARCINOMA AND CUSHING'S SYNDROME

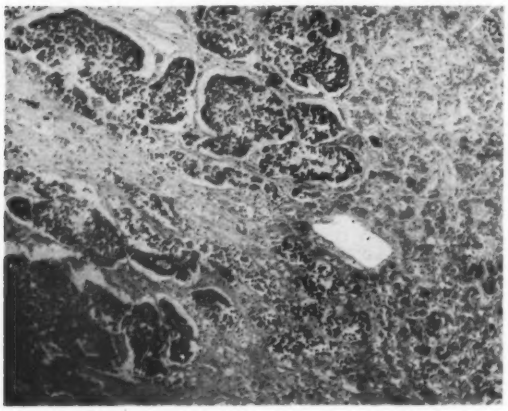


FIG. 1.—Case 2. Secondary carcinoma in adrenal gland. (H. and E. ×45.)

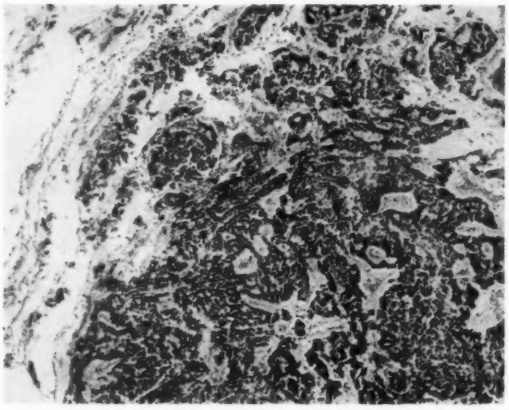


FIG. 2.—Primary bronchial carcinoma. (H. and E. ×45.)

J. K. DAWBORN *ET AL.*: ACUTE CARBON TETRACHLORIDE POISONING

FIG. 1.—Liver biopsy obtained on ninth day after swallowing carbon tetrachloride. There is pronounced centrilobular zonal necrosis. (Periodic acid–Schiff. ×80.)

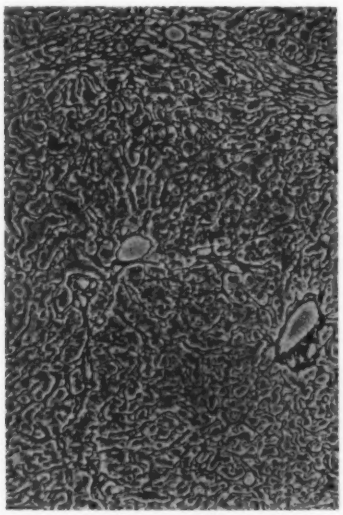


FIG. 2.—Section of liver biopsy obtained on ninth day, showing preservation of reticulin framework despite cellular necrosis. (Silver impregnation stain. ×80.)

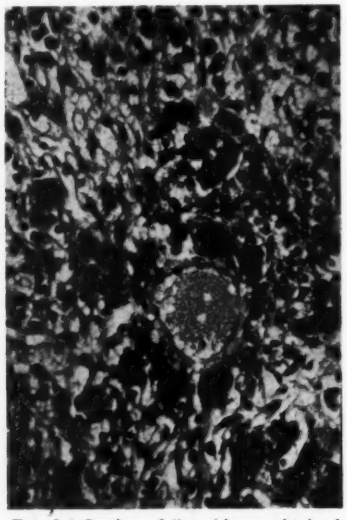


FIG. 3.—Section of liver biopsy obtained on 28th day. There are large regenerating liver cells with hyperchromatic nuclei and considerable inflammatory-cell infiltrate. Final biopsy on 70th day showed restoration of normal liver histology. (H. and E. ×400.)

C. N. BEST AND P. B. COOK: MESENTERIC RETICULOSARCOMA AND STEATORRHOEA

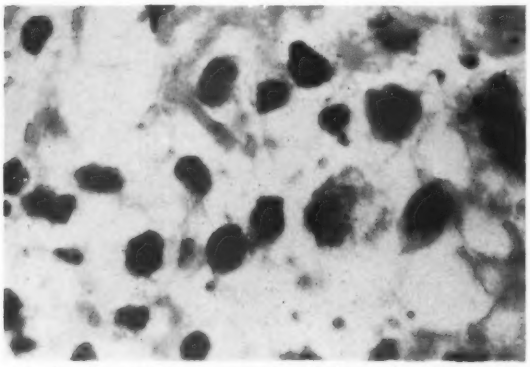


FIG. 1.—Mass of largely necrotic reticulum cells. (H. and E. ×700.)

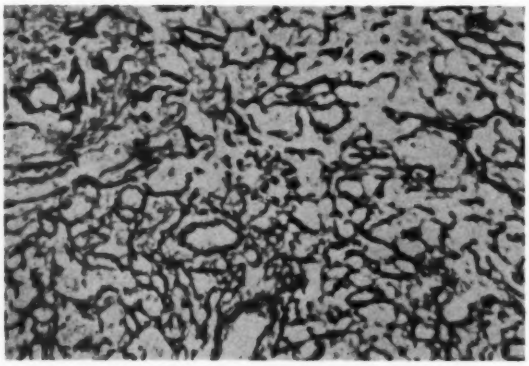


FIG. 2.—Reticulin preparation, showing dense network. (×130.)

made of two pieces, the head having been screwed on to the nail. When the heads were unscrewed a small quantity of grey-green powder and some metal particles were found to be trapped in the threads. To reduce the risk of corrosion, all implants should be cleaned by one of the established methods ; this is particularly important in the case of composite hollow implants. All the nails were inserted between 1954 and 1959 and remained in the body for periods between 18 days and five years. The patients varied in age between 15 and 82 years, the average age being 64 years. The nails were used for fractures of the femoral neck (23), slipped femoral epiphysis (2), arthrodesis of the hip (1), osteotomy (1), and arthrodesis of the shoulder (1). The reasons for removal of the nails are given in Table V. More details concerning the corroded nails and the reasons for their removal appear in Table VI.

A typical example of corrosion of a two-piece nail was shown by A.7, the head of which is illustrated in Fig. C. Corrosion had taken place at the junction between the head and stem, as reproduced at higher magnification in Fig. D. A section through the junction is shown in Fig. E. Though in this particular example corrosion had occurred only at the outer surface, a gap, such as can be seen in Fig. F, between the threaded portion of the stem and head favours corrosion of the "shielded type." Nineteen of the nails were extruded, and it was usually found at operation that the implant was quite loose in the femoral neck. This extrusion was associated with infection in three cases and with avascular necrosis of the femoral head in five cases. By virtue of its weight, shape, and the position in which it is inserted, a hip nail is liable to extrude, and this tendency is accentuated by the inevitable vibration present in a living organism. As with the 18/8 implants, there was no correlation between visible corrosion and the radiographic appearances and clinical histories of the patients.

TABLE V.—*Reasons for Removal of* 18/8/*Mo Nails*

Principal Reason for Removal	No. of Nails	No. of Nails Corroded
Simple extrusion	11*	3
Extrusion and infection	3	—
Extrusion with avascular necrosis	5	1†
Non-union	2	1
Non-union with penetration into acetabulum	2	1
Avascular necrosis	1	1
Routine	2	1†
Refracture of femoral neck due to fall	1	—
Pain	1	1
Total	28	9

* Including nail used for arthrodesis of shoulder. † Pidcock pin only.

18/8/Mo Alloy and 18/8 Alloy Mixed

There was one nail manufactured of two pieces in which the head had been made from 18/8/Mo alloy and the stem from 18/8 alloy. The head of the nail was marked with the code letter for 18/8 alloy. There was slight pitting corrosion on the threads within the head. The nail had been used in a male aged 41 years for arthrodesis of the hip, and was removed after 34 months because of gradual extrusion of the nail and the presence of a discharging sinus leading down to the implant. The organism isolated was a coagulase-negative staphylococcus. There was a small area of rarefaction in the

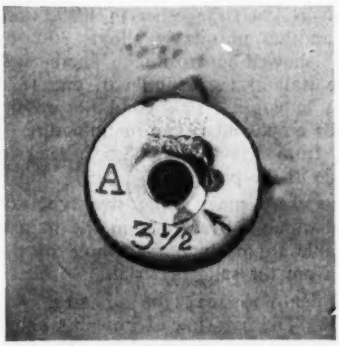


FIG. C.

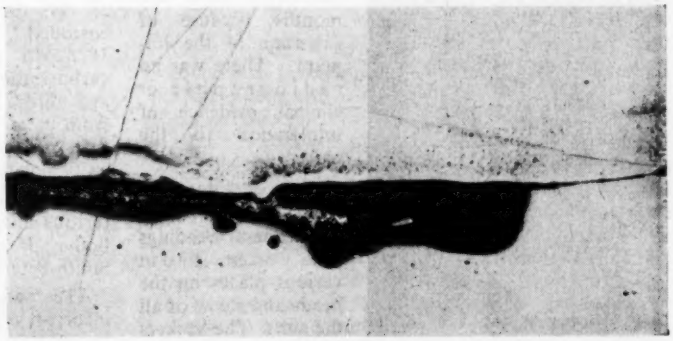


FIG. D.

FIG. C.—Nail A.7. (Maker's name removed.) Corrosion at junction between head and stem of 18/8/Mo nail (arrowed). Marks at 3 and 5 o'clock are initial spark spectroscopy burn marks. After sectioning composition of head and stem was confirmed. (×2.) FIG. D.—Nail A.7. Showing corrosion (×100) at junction of head with stem at site indicated by arrow in Fig. C.

TABLE VI.—*Situation of Corrosion and Reason for Removal of* 18/8/*Mo Nails*

Nail No.	Date Inserted	Time in Body (Months)	Construction of Nail	Situation of Corrosion	Condition Treated	Reason for Removal
A.7	1954	10	Two-piece: head 18/8/Mo; stem 18/8/Mo	Junction of stem with head	Slipped femoral epiphysis (R)	Avascular necrosis of femoral head
A.327	1957	6	One-piece	Carburization of cannula wall and pits on head surface	Fractured neck of femur (R)	Non-union with penetration into acetabulum
A.392	1956	17	Two-piece: head 18/8/Mo; stem 18/8/Mo	Corrosion of threads of stem and head	,, ,, ,, (L)	Simple extrusion
A.432	1958	½	One-piece	Pits in cannula	,, ,, ,, (R)	,, ,,
A.462	1956	24	One-piece + 18/8/Mo Pidcock pin	Pitting on Pidcock pin	,, ,, ,, (L)	Routine
A.594	1958	15	,, ,, ,,	Pitting with fracture of Pidcock pin	,, ,, ,, (L)	Extrusion with avascular necrosis
A.691	1959	10	One-piece	Shallow pitting on one flange near head	Perthes's disease (osteotomy) (L)	Pain
A.695	1958	20	,,	Carburization of cannula	Fractured neck of femur (R)	Non-union
A.704	1957	1	,,	Carburization of cannula and corrosion in areas showing impactor marks	,, ,, ,, (R)	Simple extrusion

bone over the superior border of the nail in the lateral cortex seen in a radiograph taken 31 months after operation.

Group 3: Cobalt–Chromium–Molybdenum Alloy

Two nails made from Co–Cr–Mo alloy were examined. There was no sign of corrosion on either of these nails. Both had been used for fixation of fractures of the femoral neck in patients aged 53 and 56 years

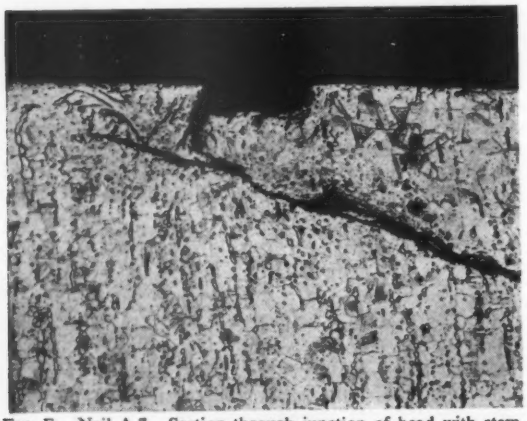


FIG. E.—Nail A.7. Section through junction of head with stem. (×150.)

FIG. F.—Nail A.7. Gap between threads of head and nail. Contained blackish powder with metal particles.

respectively, and were removed after five months and 28 months because of extrusion of the implant. There was no radiographic or clinical evidence of intolerance to the nails.

Hardness

Hardness readings were taken from various places on the heads and stems of all the nails. The Vickers "diamond pyramid" hardness number on the stem of the majority of austenitic nails lay between 150 and 270. This approximately corresponds to a tensile-strength range between 33 and 59 tons per square inch (52 and 93 kg. per sq. mm.). It was found, however, that there was considerable variation in hardness on different areas of an implant. For example, in one 18/8 nail the head gave readings of 316–317 and the stem 168–175. The steel as supplied will usually be in the softened condition, but any of the manufacturing processes—for example, grinding, milling, and polishing—will cause local increase in hardness. The hardness of the head will be increased when the nail is hammered into the femur. This was confirmed on a new 18/8/Mo nail, the hardness of the head being raised from 190–205 to 262–306 by a single blow of the hammer.

The effect of work hardening may be illustrated by a series of readings from a piece of En.58J (18/8/Mo) steel sheet. As supplied this had a polished surface (hardness 160–178; 48 readings) and an unpolished surface (hardness 155–169; 48 readings). After lightly filing the polished surface (30 strokes with moderate pressure with a No. 1 cross-cut file) the hardness increased to 164–197 (40 readings). Local differences in the physico-chemical properties of the surface of the implant can thus be caused by work hardening produced during manufacture, by hammering at insertion of the implant, and by stresses in the body which may cause the nail to bend. There was no evidence that local differences in hardness led to visible corrosion on the implants we have examined.

Mismarking

Spark spectroscopy established that a number of the implants had been mismarked by the manufacturer: eight one-piece 18/8/Mo nails marked for 18/8; one one-piece 18/8 nail marked for 18/8/Mo; two one-piece 18/8/Ti nails marked for 18/8; one 18/8/Mo head on 18/8 stem—head marked for 18/8.

Summary

Sixty-five Smith-Petersen type hip nails and four Pidcock pins removed from patients have been examined. Corrosion was detected on 26 nails and three Pidcock pins. Most of the implants were removed for reasons other than corrosion, but in at least three cases corrosion was the reason for removal.

13% Cr implants which should have been discarded before 1940 had been used in nine patients, the most recent case having been treated in 1959; all the nails were found to be corroded. Two nails of 17% Cr, 2% Ni, one inserted in 1947, the other in 1959, were corroded. This is another unsuitable alloy. 30% of 18/8/Mo implants showed corrosion. There was carburization of the wall of the cannula of one 18/8 and three 18/8/Mo implants. This condition results from certain methods employed in the manufacture of thick-walled tubing from which some Smith-Petersen nails have been made in the past.

The steel implants were made from five types of ferrous alloy, all of which can corrode in the human body. It is preferable to machine the whole of the Smith-Petersen nail from the solid material.

The code letter denoting the type of steel was incorrect on 11 nails. The marking of implants either by punching or by electrolytic methods has not predisposed to corrosion.

The corrosion resistance of the high-alloy steels examined does not appear to be related to hardness or to local variations of hardness.

We would like to thank the following for the supply of implants, case histories, and radiographs which formed the material for this investigation: D. M. Brooks, H. Jackson Burrows, J. W. Dickson, A. T. Fripp, J. I. P. James, A. P. Kitchin, C. W. S. F. Manning, P. H. Newman, K. I. Nissen, R. Y. Paton, J. H. Penrose, H. J. Seddon, D. Trevor, and J. N. Wilson. The help we have received from many registrars and the staff of medical records departments of a number of hospitals is gratefully acknowledged. We are indebted to the General Electric Company, Applied Electronics Laboratory, Stanmore, for their co-operation in certain aspects of this work. We would like to thank Miss R. Chomed, Department of Biomechanics and Surgical Materials, for her secretarial efforts in the whole investigation.

REFERENCE

Scales, J. T., Winter, G. D., and Shirley, H. T. (1959). *J. Bone Jt Surg.*, **41B**, 810.

REVERSED-EAR SYNDROME AND THE MECHANISM OF BAROTRAUMA

BY

ANTONY JARRETT, M.Sc., M.B.
Surgeon Lieutenant, R.N.

"Reversed ear" is a term which has long been current among professional divers, but the first medical description was published this year after observations on naval frogmen (Jarrett, 1961). Divers have assumed that the injury is *outward* bulging and rupture of the drum (Cousteau, 1953), but in fact the drum is never involved, and the condition is one of barotrauma to the external auditory canal.

The external pressure encountered in diving tends to push the drum inwards, a tendency which must be counteracted by blowing air through the eustachian tubes by the Valsalva manœuvre. Failure to clear the ears in this way causes *inward* rupture of the drum, not an uncommon injury among divers but clinically quite distinct from reversed ear, which is caused by totally different factors. The distinction between ruptured ear-drum and reversed ear is important, as the prognoses are so different; as amateur skin-diving is so rapidly becoming popular both conditions are likely to be seen more often in civilian practice.

The mechanism of reversed ear is particularly interesting as it throws light on the mechanism of barotrauma in general, whether caused by diving or flying, whether affecting the ears, the sinuses, or the lungs.

Clinical Observations

Fourteen cases of reversed ear were seen in a group of naval frogmen during the last four months of 1960, an overall incidence of roughly 0.5% of all dives made by the group during this period. There are no symptoms of reversed ear. In some cases the diver remembered some temporary difficulty in clearing his ears during descent; this is so common in all divers that it cannot be specifically related to reversed ear, and 9 of the 14 cases had no pain or difficulty of any kind. The gross sign of reversed ear is blood on the pinna, but lesser signs may coexist with this or be found in its absence. Twenty-volume hydrogen peroxide is useful for clearing blood and debris from the ear and making a detailed examination possible, and was incidentally found to reduce the average recovery time from 14 days (4 cases, mean deviation 3 days) to 6 days (9 cases, mean deviation 1.6 days). When the ear has been cleared one or more of three abnormalities may be seen. There may be subcutaneous petechiae in the meatus, or these may have progressed to blood-filled subcutaneous blisters which may be large enough to fill most of the lumen (Fig. 1).

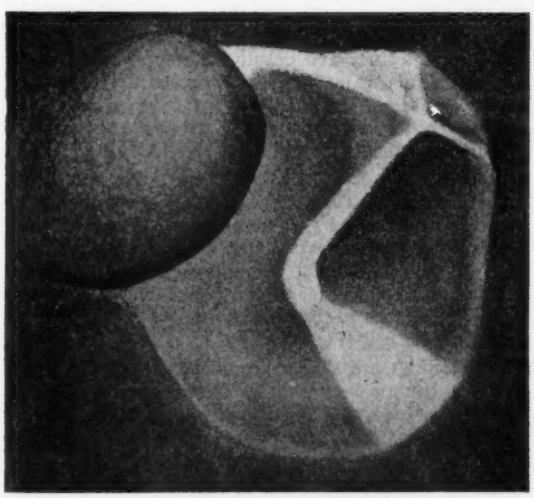


FIG. 1.—Haemorrhagic bulla arising from supero-posterior part of right external meatus.

If blood has appeared on the outer ear one such blister is oozing or has burst, and in this case ragged curtains of skin are seen surrounding a bleeding area devoid of skin. In those cases with petechiae only or in which the blisters had burst there was an unobstructed view of the drumhead, and in no case was any abnormality seen—it was always intact and freely mobile both by the Valsalva manœuvre and by Siegle insufflation. In only one case was the drum indirectly involved; a haemorrhagic blister arising from the postero-inferior part of the bony canal had extended medially, lifting the skin from the periosteum and eventually extending between the cutaneous and fibrous layers of the drum in its postero-inferior sixth. The rest of the drum was normal, and indeed the whole tympanic membrane moved normally with the Valsalva manœuvre, though the diver felt that his ear was not clearing properly. In three other cases divers said that their affected ears would not clear, but irrigating the meatus with hydrogen peroxide abolished this sensation, which was presumably due to debris resting on the drumhead.

Treatment

In cases of reversed ear, diving must be forbidden till healing is complete or petechiae may progress to bullae. It is most important to prevent infection of the damaged meatus. Hydrogen peroxide was the only local agent used, and those affected were told to keep the water out of their ears when washing and to avoid the apparently archetypal impulse to stuff them with cotton-wool. All the cases in this series were also given prophylactic sulphadimidine, 1 g. t.d.s.; but the necessity for this is speculative, as there were no controls. Infection did not occur in any of the cases, and all but one were completely healed within two weeks of injury. The only case to persist beyond this period was that in which blood had extended between the layers of the drum, where it formed a clot which remained for over six weeks.

Aetiology

The body fluids are incompressible, and any increase in pressure is transmitted equally without any tendency to compress or distort. Air, on the other hand, is compressible, and to prevent the distortion or collapse of the respiratory tract and its appendages the air within them must be kept at the external pressure. When the pressure everywhere in the body is the same—in air spaces and in tissue fluid—body sensation and function are quite unaffected.

Modern divers achieve this by breathing air which is automatically regulated to the external pressure no matter how this changes; this ensures that the air in the lungs, paranasal sinuses, and middle-ear spaces will always be at the external pressure (Fig. 2), provided the

ears are cleared and the ostia of the sinuses patent. Their equipment is completed by a flexible rubber suit and hood, which should transmit the external pressure to every other part of the body (Fig. 3). Unfortunately, watertight rubber suits do not seem to do their job properly, for during and after a dive there is a most noticeable partial vacuum within the suit—invariably the first act on leaving the water is to pull the hood away from the face to let in a rush of air. This lowered pressure in the suit and meatus would certainly cause the drum to bulge outwards, but this in itself is harmless; it occurs in the Valsalva manœuvre, which never causes pain or damage to a healthy drum (Mr. John F. Simpson, personal communication) even though intratracheal pressures of 450 mm. Hg may be produced (Faulkner and Sharpey-Schafer, 1959). However, this does not dispose of the lowered meatal pressure as a possible cause of reversed ear.

An increased external pressure has an effect which is often overlooked. As the body is immersed in water the blood-pressure is increased by the pressure of the water by direct fluid transmission. Of course, the systolic/diastolic difference remains the same, and as the tissue fluid pressure is also increased by the external pressure the peripheral resistance and work of the heart remain almost unchanged—they are in fact slightly lowered owing to the reduced head of hydrostatic pressure within the vascular system. But, as we have seen, the pressure within a watertight rubber suit, and therefore in the external meatus, is less than the external pressure, and the increased blood-pressure will tend to passively dilate the blood-vessels on the surface of the body. Actual dilatation cannot occur where the surface of the body is supported by the external pressure through the direct contact of the suit, but, of course, there is no such contact or support for the skin of the external meatus. The skin in this situation is closely attached to the periosteum, and there is very little elastic subcutaneous tissue in which the vessels of the rete arteriosum cutaneum can expand. Any tendency to do so will split the skin from the periosteum, forming first petechiae then bullae—precisely the damage seen in reversed ear.

FIG. 3.—Watertight rubber suit showing face and cuff seals.

It was decided to test this hypothesis by measuring the extent of the partial vacuum in a suit during a dive, and seeing whether this order of negative pressure would produce the damage seen in reversed ear when applied to the meatus under experimental conditions.

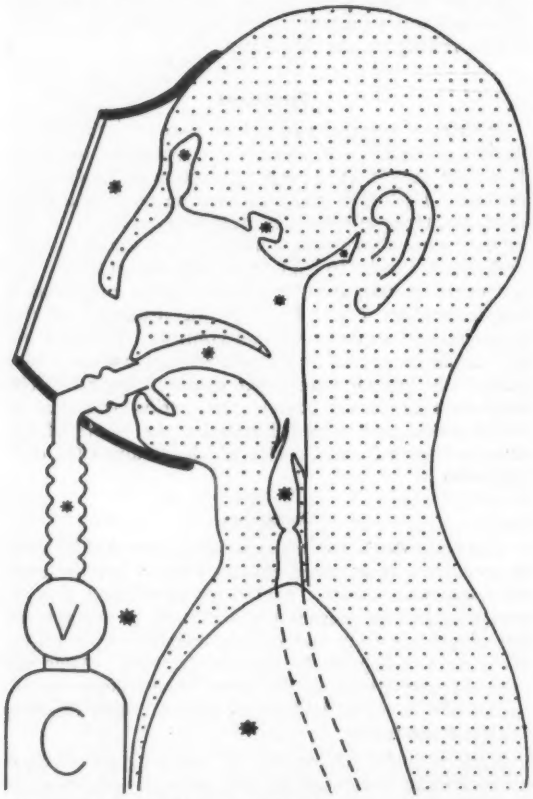


FIG. 2.—Valve V always supplies air at pressure of water surrounding it—all parts marked with an asterisk are at same pressure. The stippled area represents tissue fluid at pressure of surrounding water. (C=cylinder.)

Experimental Observations

The usual diving-dress comprises a suit and a hood which are clamped together so that the space within is continuous over the whole head and body, but excluding the hands and face (Fig. 3). For the following experiments a special neck seal was worn instead of the hood to exclude the ears from the partial vacuum formed in the suit and avoid damage to them. The suit was connected to a pressure gauge with the zero adjusted to allow both positive and negative pressures to be read; it was recalibrated in a pressure-chamber. The exterior of the Bourdon tube was exposed so that the gauge would register the *difference* between the external pressure and that within the suit.

Four dives to 80 ft. (24.4 m.) were made, measuring depth at the subject's suprasternal notch, and the gauge reading was recorded at intervals of 10 ft. (3 m.). For convenience these dives were made in an open diving-bell in which the subject was submerged to the suprasternal notch; this made diving-masks unnecessary and allowed the gauge to function normally in the pocket of air under the bell (Fig. 4).

The findings are shown graphically in Fig. 5, from which it can be seen that as the depth of the dive increases so does the partial vacuum within the suit, reaching a maximum under these conditions of −12.75 lb./sq. in. (−0.896 kg./sq. cm. or −659 mm. Hg). The graph does not pass through the origin, for as the diver submerges some air is squeezed from his suit through the cuffs and neck seal. This permanent diminution in

the volume of the suit is resisted by the elasticity of its material and gives rise to the residual partial vacuum of some −10 mm. Hg, which is determined solely by the degree of venting and not by the depth of the dive. *It is, of course, this same elastic resistance to compression which causes the partial vacuum within the suit throughout the dive.*

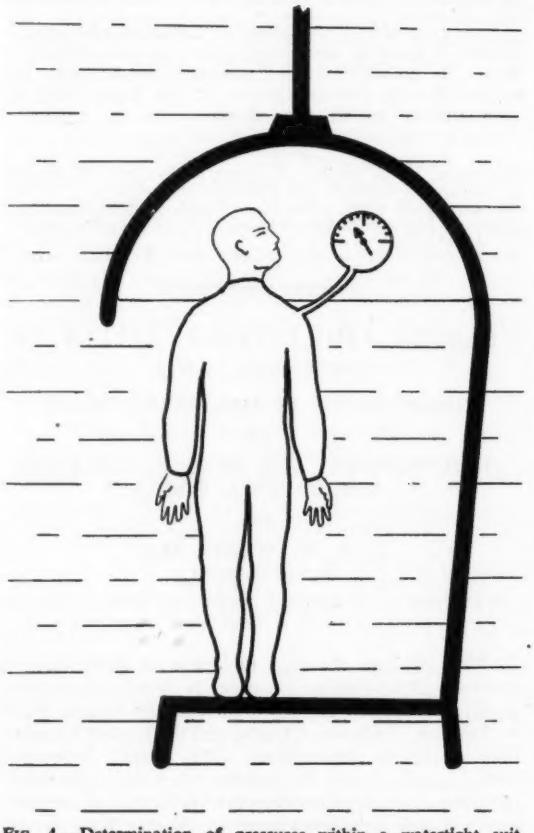


FIG. 4.—Determination of pressures within a watertight suit, using an open diving-bell.

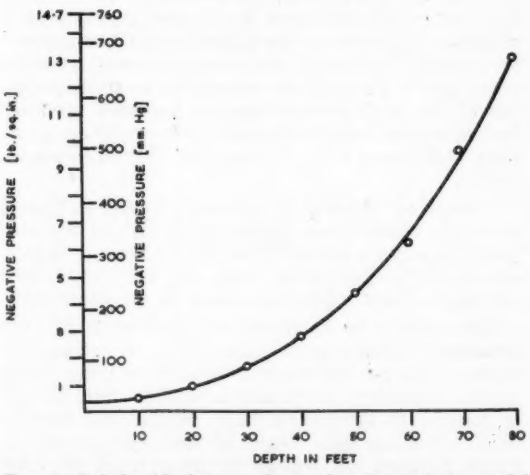


FIG. 5.—Relationship between depth of a dive and the partial vacuum existing within the suit. Observations in four determinations were identical, variation being less than the discrimination of the gauge. (0.25 lb./sq. in.)

Having determined the negative pressure occurring in a diving-suit it remained to apply negative pressures of this order to the external meatus while observing it continuously for signs of damage. This was achieved by attaching a pressure-sealed Siegle's speculum to the upper end of a mercury manometer. The speculum was applied to the subject's meatus and sealed in with petroleum jelly, while the meatus and the drum were observed by myself with the aid of a headlight (Fig. 6), while the whole set-up — subject, speculum, manometer, and observer — was contained in a large compression chamber. When the pressure in this was gradually increased it acted on everything within it except the subject's external meatus, which had been sealed off in the way described. The extent of the partial vacuum within the meatus was directly recorded by the manometer.

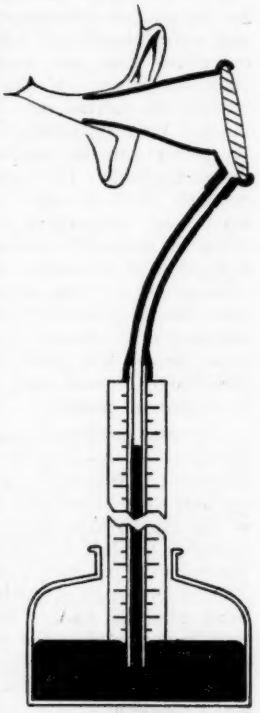


FIG. 6.—Arrangement used to observe the meatus while at a pressure below ambient. Both subject and observer were in a compression chamber throughout.

In the first experiment the pressure in the chamber was increased till the manometer stood at 120 mm. Hg. At this point the drum was only slightly injected along the handle of the malleus though bulging outwards most markedly, and the experiment was terminated as bright red petechiae had appeared in the swollen meatal walls. In a second experiment petechiae appeared in the meatal walls at 150 mm. Hg negative pressure, but before pressure could be restored to normal several postero-superior petechiae had coalesced to form a haemorrhagic bulla about 7 mm. in diameter. In both cases the tympanic membrane appeared quite normal on returning to atmospheric pressure. Only the petechiae and bulla persisted, the oedema of the meatal walls disappearing as the negative pressure was released. No skin was broken, and both ears were completely normal in four days.

The pressure causing this damage corresponds to the partial vacuum within a suit when diving 30 to 50 ft. (9 to 15 m.) below the surface, which is in fact the depth range at which the great majority of cases of reversed ear do occur.

Discussion

The basic cause of the reversed-ear syndrome is that the watertight rubber suit converts the external meatus into a closed cavity within which the pressure may fall below that of the body tissues. When this happens the blood-vessels in the skin of the meatus are passively dilated by the excess blood-pressure, with resultant dilatation and rupture. This situation can be generalized; if in any body cavity the pressure falls below that of the body tissue (which is always equal to the

external pressure by direct fluid transmission) the vessels lining the cavity will respond in the same way.

The best-known situation in which this occurs is the middle-ear cavity when descending in an aircraft. While at altitude the pressure in the middle ear falls, as air can always escape passively from the eustachian tube. As the aircraft descends the barometric pressure rises, and unfortunately air will not passively re-enter the eustachian tube but must be made to do so by a conscious effort. If this effort is not made or is inefficiently carried out, or if the eustachian tube is blocked by an infection of the upper respiratory tract, the pressure in the middle ear falls below that in the rest of the body. The vessels in the middle ear are then passively dilated, with consequent reddening of the drum and transudate into the middle-ear cavity, so-called aero-otitis media (Armstrong, 1939). The indrawing of the drum which occurs is a mechanical concomitant of these effects and not their cause. Its main danger is that rupture occurs when the mechanical tolerance of the drum is exceeded, but pain and deafness occur before this limit has been reached and, most significantly, remain long after the drum has returned to its normal position.

The same mechanism explains the haemoptysis which sometimes occurs in those who dive without breathing apparatus. When diving with the breath held the thoracic cage must collapse to equalize the pressure in the lungs; this process is limited when the lungs approach residual volume. If the diver descends below this point the pulmonary vessels dilate and may rupture. This injury occurs in native pearl-divers and skin-divers using schnorkel masks. Infection of the upper respiratory tract may close the ostia of the paranasal sinuses, converting them into closed spaces in which a falling pressure can cause similar bleeding in addition to pain and congestion.

The danger of reversed ear is created by anything which closes off the external auditory canal, and ear-plugs are worse in this respect than a frogman's suit. They should never be worn when diving or when travelling by air; when descending in either situation they may not only cause reversed-ear injury but may be driven inwards by the increasing pressure and cause direct trauma of the drum. If an amateur skin-diver wishes to wear a suit in cold waters he should choose one made of porous rubber. This will never cause reversed ear, as a porous material cannot possibly maintain a partial vacuum, and the petechiae which form in the skin under the wrinkles of a watertight suit are, of course, never seen. A porous type of suit maintains body temperature quite efficiently, as it fills with and holds water in the same way as a woollen garment normally fills with and holds air.

Barotrauma may occur in other artificial cavities; some goggles worn by amateur skin-divers form a closed cavity in front of the eyes, and diving in these has caused serious conjunctival haemorrhage. Goggles worn for this purpose should cover the nose as well as the eyes so that air can be blown into them to equalize pressures during descent.

Summary

The clinical features, treatment, and prevention of the reversed-ear syndrome are discussed. It is a condition of barotrauma to the external auditory canal and is characterized by petechiae, bullae, and rupture of the skin in the meatus. It occurs when the pressure in the external canal falls 100–200 mm. Hg below that in the body tissues, in which circumstance the blood-vessels in the skin will be passively dilated to give rise to these signs. The syndrome has been produced and observed experimentally since its original observation among professional divers. Similar injury will occur in any body cavity which falls below external pressure, and the significance of this in aviation and diving is discussed.

I am grateful to Petty Officer H. Eccleston, who acted as subject in some of these experiments; to Petty Officer G. Brown for his assistance and musical accompaniment; and to the Medical Director-General of the Royal Navy for permission to publish these findings.

REFERENCES

Armstrong, H. G. (1939). *Principles and Practice of Aviation Medicine*. Williams and Williams, Baltimore.
Cousteau, J. Y. (1952). *The Silent World*. Hamish Hamilton.
Faulkner, M., and Sharpey-Schafer, E. P. (1959). *Brit. med. J.*, 1, 685.
Jarrett, A. S. (1961). *J. roy. nav. med. Serv.*, 47, 13.

PLASMA CHOLESTEROL LEVELS IN NEW ZEALAND

OBSERVATIONS IN 1,000 URBAN MALES

BY

J. D. HUNTER, M.B., M.R.C.P., M.R.A.C.P.
Senior Lecturer in Medicine

AND

L. C. K. WONG, M.Sc.
Research Assistant

Department of Medicine, University of Otago, Dunedin, New Zealand

In New Zealand the high incidence of deaths due to coronary artery disease is similar to that found in other highly westernized countries such as the United States of America, Australia, Canada, and the United Kingdom (World Health Organization 1955, 1956). Numerous well-planned surveys throughout the world have shown the close association between the prevalence of coronary artery disease in a population on the one hand and the mean blood cholesterol concentrations on the other (Keys *et al.*, 1952, 1958; Bronte-Stewart *et al.*, 1955). Relatively high cholesterol levels have been found in inhabitants of some of the aforementioned countries—for example, the United States and the United Kingdom—and also in Finland. In populations so characterized, one of the most constant features has been the trend for cholesterol levels to increase with age (Keys *et al.*, 1950, 1958; Keys, 1956; Lawry *et al.*, 1957; Lewis *et al.*, 1957).

From New Zealand—a country reputed to have a *per capita* consumption of total fat as high as or higher than in any other nation (Food and Agriculture Organization, 1955)—there have been no previous surveys relating to blood cholesterol values in the population.

The study to be described was undertaken in 1,000 apparently healthy adult males from an urban community. The purpose was to determine the mean fasting plasma cholesterol levels and to analyse such findings in relation to occupation, body weight, and smoking habits at various ages. While, as might be expected, the major findings are similar to those noted in other westernized communities, there are certain features which differ and give food for further thought.

Materials and Methods

The 1,000 male subjects, aged from under 20 to over 60 years, were all symptom-free, apparently healthy, and actively employed. They came from two large broad occupational groups, 500 being manual workers in one industrial concern (manufacturing railway locomotives and equipment), the other 500 from sedentary and semi-sedentary occupations of varying nature—professions, business executives, accountants, clerks, shopkeepers, taxi-drivers, school teachers, students, etc. — all volunteers.

Besides age and occupation, a record was made of height to the nearest half-inch and of weight (stripped) to the nearest pound, and smoking habits were standardized to the number of cigarettes per week. Oxalated blood samples were taken at 8 a.m. with the subjects in the fasting state for at least 10 hours. Total plasma cholesterol concentrations were estimated in duplicate—individually by both of us—using the method of Zlatkis *et al.* (1953) as modified by MacIntyre and Ralston (1954), and a mean of the duplicate was taken as the final value. Between groups of 50 duplicate observations there was a standard error of 6.53 mg.

Results

Mean Plasma Cholesterol Levels and Age

The mean levels according to five-year age-groups are shown in Table I. There is a wide but consistent

TABLE I.—*Plasma Cholesterol Levels in* 1,000 *Apparently Healthy New Zealand Males (Urban Community)*

Age-group	No.	Mean Cholesterol Level (mg./100 ml.)	S.D.	Coefficient of Variation
15–19 years ..	75	187	33·3	18%
20–24 ,, ..	138	207	37·9	18%
25–29 ,, ..	87	221	39·1	18%
30–34 ,, ..	112	231	39·4	17%
35–39 ,, ..	117	242	40·3	17%
40–44 ,, ..	110	247	37·3	15%
45–49 ,, ..	160	248	39·6	16%
50–54 ,, ..	128	243	38·9	16%
55–59 ,, ..	52	240	37·5	16%
60–64 ,, ..	14	236	39·5	17%
65–69 ,, ..	7	215	35·5	17%
Total ..	1,000	231	42·6	18%

standard deviation for each group. The mean level for 1,000 males for all ages is 231 mg./100 ml. However, from a mean level of 187 mg./100 ml. in age-group 15–19 there is a progressive increase in levels with age to a maximum mean of 248 mg. in age-group 45–49. Thereafter, as illustrated in the fitted-trend curve (Fig. 1), from a turning point calculated to be around 47 years of age there is a subsequent slight decline in values.

Occupation

According to age, the mean levels in 500 industrial manual workers are compared with the levels observed in the composite 500 sedentary and semi-sedentary group ("white-collar" workers) (Table II and Fig. 2).

TABLE II.—*Comparison of Mean Plasma Cholesterols in the Two Main Occupational Groups*

Age-group	Industrial Workers No.	Industrial Workers Mean Cholesterol Level (mg./100/ml.)	White-collar Group No.	White-collar Group Mean Cholesterol Level (mg./100/ml.)	Student's "t"
15–19 years	48	180	27	200	$t=2·63$; d.f.=73 $0·01<P<0·02$**
20–24 ,,	70	201 } 205	68	212 } 219	$t=2·90$; d.f.=223 $0·001<P<0·01$**
25–29 ,,	39	211 }	48	230 }	
30–34 ,,	52	222 } 229	60	239 } 244	$t=2·85$; d.f.=227 $0·001<P<0·01$**
35–39 ,,	59	236 }	58	249 }	
40–44 ,,	47	244 } 243	63	250 } 251	$t=1·79$; d.f.=268 $0·05<P<0·10$
45–49 ,,	80	242 }	80	253 }	
50–54 ,,	66	238 } 238	62	248 } 246	$t=1·48$; d.f.=178 $0·10<P<0·20$
55–59 ,,	28	238 }	24	242 }	
60–64 ,,	7	224 } 228	7	247 } 229	$t=0·03$; d.f.=19 $0·90<P$
65–69 ,,	4	236 }	3	187 }	
Total	500	224	500	238	$t=5·24$; d.f.=998 $P<0·001$***

The overall mean cholesterol levels for the two general occupational groups are 224 mg./100 ml. for the industrial workers and 238 mg./100 ml. for the white-collar workers. The decade levels in the white-collar group exceed those in the industrial group throughout. The differences in values, particularly noticeable in the younger age-groups, are highly significant both in the total sample and in the decades below 40 years of age (see P values in Table II).

Relative Weight

At the time of the study the degree of obesity of subjects could not be measured more directly. Relative weights, estimated to obtain a crude sample of overweight individuals at one end of the scale, were evaluated by taking the actual weight of each subject expressed as a percentage of the so-called standard weight for a man at that age and height. Standard weights were obtained from the tables for weight and age of the Metropolitan Life Insurance Company of the U.S.A. Although these figures are based on American standards we have taken them as a useful dividing line to classify our subjects into low, medium, and high relative weights; in particular to separate off the high-relative-weight group, who, as others have indicated, consist largely of the clinically obese subjects. In this series this group constituted approximately 10% of the total sample and were distributed approximately

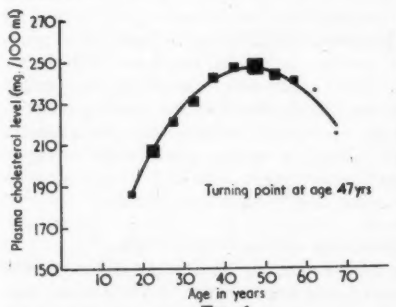


FIG. 1

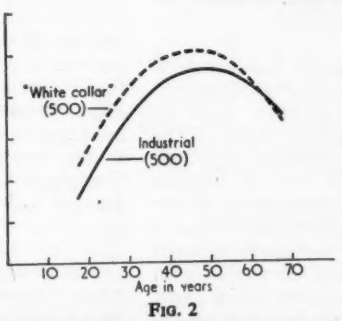


FIG. 2

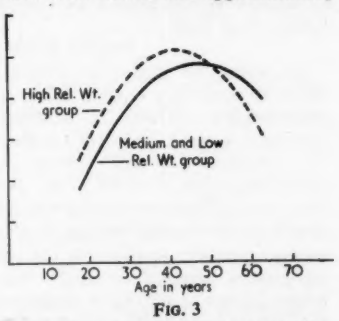


FIG. 3

FIG. 1.—Plasma cholesterol change with age in 1,000 New Zealand males. FIG. 2.—Mean plasma cholesterols in two main occupational groups. (Fitted-trend curves.) FIG. 3.—Mean plasma cholesterol levels according to relative weights. (Fitted-trend curves.)

equally in the two occupational groups. Thus *high*-relative-weight (overweight) subjects had weights over 120% of the standard weight, *medium* were between 120% and standard, and *low* were under the standard weight.

In view of the method used to assess overweight it was thought justifiable only to compare the cholesterol levels of the high-relative-weight group with the low- and medium-relative-weight groups combined. Comparison by five-year age-groups showed that in the groups below 40 years of age the mean levels in the overweight subjects exceeded those in the remainder but not to a statistically significant degree. At ages of 40 years and above there were no such differences.

If the total sample is examined—omitting 31 subjects in whom data were incomplete, those aged 60 and over because of insufficient numbers and those under 20 because they were regarded as actively growing—then in the 20–59 year age sample of 873 subjects the mean cholesterol level of 84 overweight subjects (243 mg./100 ml.) exceeds that in the rest (234 mg./100 ml.), but again not to a highly significant degree. However, as shown in Table III, if a division of this whole 20–59-year age sample is made equally by age into an older sample of 40 and above and a younger sample below 40 years, then comparison of the mean cholesterol levels between the overweight group and the combined low- and medium-relative-weight groups reveals highly significant findings dependent upon age. Whereas in the older (40–59-year sample) there is no difference in levels between the overweight and the rest —244 mg./100 ml. in both groups—in the younger (20–39-year sample) the overweight subjects have a mean cholesterol level of 241 mg./100 ml. compared with 223 mg./100 ml. in the rest, a difference which is highly significant in that the probability that this has occurred by chance is less than 1 in 100 but greater than 1 in 1,000.

TABLE III.—*Relative Weights and Mean Cholesterol Levels*

Relative Weight Group	No.	Mean Cholesterol Level (mg./100 ml.)		
A. All Age Groups 20–59 Years				
High	84	243		$t = 1{\cdot}88$; d.f. = 871
Medium	437	234	234	$0{\cdot}05 < P < 0{\cdot}10$
Low	352	233		
B. Older Age-groups 40–59 Years				
High	40	244		$t = 0{\cdot}08$; d.f. = 433
Medium	210	246	244	$0{\cdot}9 < P$
Low	185	242		
C. Younger Age-groups 20–39 Years				
High	44	241		$t = 2{\cdot}75$; d.f. = 436
Medium	227	223	223	$0{\cdot}001 < P < 0{\cdot}01$
Low	167	222		

Smoking Habits

To assess the degree of smoking, the subjects were classified according to their habits as follows: Group A, non-smokers. Group B, smokers of from 1 to 99 cigarettes a week. Group C, smokers of from 100 to 199 cigarettes a week. Group D, smokers of 200 or more cigarettes a week. As there was an obvious deficiency of heavier smokers in the younger age-group and a proportionate excess in the older age-group, it was not possible to evaluate the effect of smoking in all age-groups together or singly—as has been done with other factors. We have therefore taken for analysis the most important age-group—that is, from 40–59 years. As within this group there is no trend of changing smoking habits with age, nor is there any overall association between overweight and tobacco smoking, it is valid to compare the various smoking categories and in the comparison any difference is not due to age or overweight. As shown in Table IV, if non-smokers are compared with smokers of all categories combined, a cholesterol mean of 248 mg./100 ml. is seen in non-smokers in contrast to a mean of 244 mg./100 ml. in the smokers—a difference which is of no significance whatsoever. Comparing non-smokers with group D or group D and C smokers combined, or comparing non-smokers and group B smokers with smokers of group C and D combined, however contrasted, no differences in mean cholesterol values can be discerned. Separate analyses for both industrial and white-collar groups showed identical findings.

TABLE IV.—*Plasma Cholesterol Levels and Smoking Habits in 450 Males Aged 40–59 Years*

Group	No.	Mean Cholesterol Levels (mg./100 ml.)		
A	159	248	248	245
B	118	240		
C	148	247	244	247
D	25	246		246

A: Non-smokers
B: 1–99
C: 100–199 } cigarettes/week
D: 200+

Discussion

Age-Trend in Cholesterol Levels

The pattern of age-trend in cholesterol levels described in this study conforms closely to that generally noted by many but not all observers in other highly westernized communities, particularly in the United States (Keys *et al.*, 1950; Lawry *et al.*, 1957; Lewis *et al.*, 1957). However, slight and possibly suggestive differences are noted.

(1) The maximum mean values obtained in this study are slightly higher than in the surveys of Lewis *et al.* (1957) and Lawry *et al.* (1957) in the United States, but they are less than the mean values reported from Finland by Keys *et al.* (1958). In view of the variability of methods of cholesterol determination between laboratories, considerable caution must be exercised in drawing any conclusions from these apparent international differences, which therefore are noted merely for what they are worth.

(2) Perhaps more significant in our survey is that with the age-trend the turning-point in our decreasing values is around 47 years, compared with around 55 years as noted by Lewis *et al.* (1957). Some have postulated that this late age-trend in mean cholesterol levels observed in surveys of this nature may be—at least partially—the consequence of excessive deaths among subjects with higher cholesterol levels, hence diminishing the mean normal levels in the later age-groups (Lawry *et al.*, 1957). On this hypothesis one might suggest further the possibility that the turning-point in our males coming some eight years before that reported in the several American series may be reflecting a "coronary loss" operating at an earlier age in New Zealand males; but this is mere speculation.

Occupation and Cholesterol Levels

The finding of distinct and significant differences in mean cholesterol levels between the two broad occupational groups is particularly interesting in view of the relationship claimed to exist between occupational

status and both coronary mortality rates and the degree of ischaemic myocardial fibrosis found at necropsy (Morris *et al.*, 1953; Morris and Crawford, 1958). As indicated in Fig. 2, the two fitted-trend curves of cholesterol levels with age show an approximation in the later decades, the turning-point for the white-collar group being earlier than that for the industrial group—that is, around 45 years, as opposed to around 48 years of age. Again, on speculation such findings might suggest disproportionate "coronary loss" from the white-collar as opposed to the industrial middle-aged group. Whether these cholesterol patterns are related to possible differences in social status, physical activity, or diet, etc., between the two groups cannot be commented on at this stage.

Overweight and Cholesterol Levels

Most published reports have indicated that serum cholesterol levels are not greatly influenced by the presence of overweight. However, there is a certain amount of evidence that an individual's serum cholesterol increases while he is actually putting on weight (Mann *et al.*, 1956; Gordon *et al.*, 1958). Although in the present study there has been no true measure of obesity, the division of subjects by relative weight has given a crude sample of overweight individuals who could be accepted as clinically obese. The positive correlation between cholesterol levels and overweight in the younger subjects in contrast with the older subjects was unexpected. The significance of this finding is a matter of conjecture. Possibly the increase in cholesterol levels in the overweights of the younger decades is related to a period of rapid weight increase. On the other hand, a positive correlation might have extended into the later decades but for the fact that a relatively greater number of overweight subjects may have developed coronary disease, leaving a residual apparently healthy sample with lower mean cholesterol levels. It is interesting that on these fitted-trend curves of cholesterol levels with age the turning-point towards decreasing levels is around 41 years in the overweight subjects compared with 47 years in the remainder. That obese subjects do succumb to coronary disease more readily seems to be very probable (Gubner, 1957; Dawber *et al.*, 1957).

Smoking Habits and Cholesterol Levels

Smoking and coronary disease have been linked together for many years, more recently since a positive relationship was indicated between them in several major statistical surveys (Doll and Hill, 1956; Hammond and Horn, 1958; Buechley *et al.*, 1958). In general it has been maintained that the coronary mortality rates for men who smoke 20 cigarettes or more daily generally exceed the corresponding rates for non-smokers.

Investigating serum cholesterol levels in relation to smoking habits, others, such as Miller *et al.* (1958) in the U.S.A. and Karvonen *et al.* (1959) in Finland, have reported significantly higher levels in smokers than in non-smokers. Our own observations are therefore in contrast to these surveys, but are consistent with the findings of Gofman *et al.* (1955), who found that although heavy smokers in the 20–39-year age-group had higher cholesterol values than non-smokers this was not so in the 40–59-year age-group. Because of the deficiency of heavy smokers in our 20–39-year age-group it has not been possible to examine for any similar age-trend in our subjects. Perhaps there is a trend dependent on age comparable to that which we have noted in respect to occupational status and overweight.

Summary

Fasting plasma cholesterol levels have been estimated in 1,000 apparently healthy New Zealand urban males, and a statistical analysis of the mean levels has been undertaken in relation to age, occupation, relative weight, and smoking habits.

The trend of mean levels rising with age to a maximum mean of 248 mg./100 ml. between 45 and 49 years of age, then of a subsequent decline, conforms to the general pattern reported by others in westernized communities, except that the turning-point towards decreasing levels occurs at an earlier age.

Mean levels in "white-collar" workers exceeded those in age-matched industrial workers under 40 years of age with highly significant differences, but there was an approximation of levels in the later decades.

Excessively overweight subjects (10% of the total as assessed by relative weights) had mean levels significantly higher than in the remaining subjects in the 20–39 years sample, this being in contrast to the finding in the 40–59 years sample, in which both the overweight and the remaining subjects had identical mean levels. No difference in mean cholesterol levels was found between non-smokers and smokers of any grade in the 40–59-year age-group.

The different age-trends in cholesterol values in relationship to general occupational status and to the presence or otherwise of overweight is discussed speculatively in respect of possible differences in coronary mortality rates in middle age. The importance of the age factor in assessing these relationships, particularly between overweight and cholesterol levels, is stressed.

We thank Dr. A. M. O. Veale and Mr. F. G. Spears for their considerable assistance in the statistical analyses, and Miss Moira Hunt and Mr. W. T. Poulsen for technical help. We are grateful to the many subjects who co-operated so willingly. The study was supported in part by the Medical Research Council of New Zealand.

References

Bronte-Stewart, B., Keys, A., and Brock, J. F. (1955). *Lancet*, **2**, 1103.

Buechley, R. W., Drake, R. M., and Breslow, L. (1958). *Circulation*, **18**, 1085.

Dawber, T. R., Moore, F. E., and Mann, G. V. (1957). *Amer. J. publ. Hlth*, **47**, 4.

Doll, R., and Hill, A. B. (1956). *Brit. med. J.*, **2**, 1071.

Food and Agriculture Organization (1955). Food Consumption Food Balance Sheets.

Gofman, J. W., Lindgren, F. T., Strisower, B., De Lalla, O. F., Glazier, F., and Tamplin, A. (1955). *Geriatrics*, **10**, 349.

Gordon, H., Wilkens, J., and Brock, J. F. (1958). *S. Afr. med. J.*, **32**, 549.

Gubner, R. S. (1957). *Nutr. Rev.* **15**, 353.

Hammond, E. C., and Horn, D. (1958). *J. Amer. med. Ass.*, **166**, 1159.

Karvonen, M., Orma, E., Keys, A., Fidanza, F., and Brozek, J. (1959). *Lancet*, **1**, 492.

Keys, A. (1956). *World Trends in Cardiology*, edited by A. Keys and P. D. White, **1**, 134. New York.

—— Fidanza, F., Scardi, V., and Bergami, G. (1952). *Lancet*, **2**, 209.

—— Karvonen, M. J., and Fidanza, F. (1958). Ibid., **2**, 175.

—— Mickelsen, O., Miller, E. V. O., Hayes, E. R., and Todd, R. L. (1950). *J. clin. Invest.*, **29**, 1347.

Lawry, E. Y., Mann, G. V., Peterson, A., Wysocki, A. P., O'Connell, R., and Stare, F. J. (1957). *Amer. J. Med.*, **22**, 605.

Lewis, L. A., Olmsted, F., Page, I. H., Lawry, E. Y., Mann, G. V., Stare, F. J., Hanig, M., Lauffer, M. A., Gordon, T., and Moore, F. E. (1957). *Circulation*, **16**, 227.

MacIntyre, I., and Ralston, M. (1954). *Biochem. J.*, **56**, XLIII.

Mann, G. V., Teel, K., Hayes, O., McNally, A., and Bruno, D. (1955). *New Engl. J. Med.*, **253**, 349.
Miller, D. C., Trulson, M. F., McCann, M. B., White, P. D., and Stare, F. J. (1958). *Ann. intern. Med.*, **49**, 1178.
Morris, J. N., and Crawford, M. D. (1958). *Brit. med. J.*, **2**, 1485.
—— Heady, J. A., Raffle, P. A. B., Roberts, C. G., and Parks, J. W. (1953). *Lancet*, **2**, 1053, 1111.
World Health Organization (1955). *Annual Epidemiological and Vital Statistics, 1952.*
—— (1956). *Epidem. vital Statist. Rep.*, 9, No. 10.
Zlatkis, A., Zak, B., and Boyle, A. J. (1953). *J. Lab. clin. Med.*, **41**, 486.

CARCINOMA AND CUSHING'S SYNDROME

BY

J. R. BILLINGHURST, B.M., M.R.C.P.
Medical Registrar, University College Hospital, London

A. K. THOULD, M.D., M.R.C.P.
Medical Registrar, University College, Hospital, London

O. P. GALPIN, M.B., M.R.C.P.
Senior Medical Registrar, Manchester Royal Infirmary

AND

J. M. HINTON, B.M., B.Ch.
House-physician, Whittington Hospital, London

[WITH SPECIAL PLATE]

Though it is common at necropsy to find adrenal metastases from primary bronchial carcinoma, these do not usually give rise to any clinically recognizable endocrine disturbance. On the other hand, patients with bronchial carcinoma may very occasionally manifest the biochemical or even full clinical features of Cushing's syndrome. This subject has recently been fully reviewed by Allott and Skelton (1960), and mention has been made of primary sites of carcinoma other than the bronchus. It is worth drawing attention to this association between carcinoma and adrenocortical overactivity, partly to avoid the erroneous diagnosis that the primary neoplasm lies in the adrenal cortex, and partly to prevent the patient undergoing a fruitless adrenalectomy when a primary neoplasm elsewhere is unsuspected. Bagshawe (1960a) has pointed out that the finding of marked hypokalaemic alkalosis in a patient with adrenocortical overactivity should arouse strong suspicion of a primary neoplasm, most commonly in the bronchus.

Two further cases of this association are reported here. In each it was considered at one time that the primary carcinoma might be present in the adrenal.

Case 1

The patient, a housewife aged 57 years, was admitted to Harefield Hospital on October 23, 1959, chiefly because of mental disturbance. Over the preceding three months there had been a gradual and progressive change of mood with alternating bouts of depression and elation, sometimes with aggressive outbursts, sometimes with grandiose delusions of wealth and largesse. The first physical symptom noticed by the patient was swelling of the legs and arms in May, 1959, followed later by swelling of the face. Treatment by diuretics led to some improvement in the arms, but her legs became progressively larger, as did her face. Her weight greatly increased and she became much more breathless on exertion. She noticed a dry mouth, but did not mention undue thirst or polyuria. There was no complaint of muscular weakness. She smoked 20 to 30 cigarettes daily, and had suffered from a cough for 20 years. No relevant past or family history was obtained.

On admission she was garrulous and sometimes confused. There was marked generalized pigmentation of the skin, largely racial in origin, but considered by her husband to have increased from its previous level. The buccal mucous membrane was not pigmented. Extensive purpura was present over both forearms, and purple striae were noted in the skin of the abdomen and buttocks. There were typical fatty deposits over the trunk, face, and neck. Hirsuties was not marked. Pitting oedema of the lower limbs was not associated with raised jugular venous pressure. The blood-pressure was 150–190/90–110 mm. Hg. Hess's capillary fragility test was negative. Crepitations were heard over the left lower lobe of the lung. Both ankle-jerks were absent, but no sensory abnormalities were detected. The urine contained 2% of sugar and a trace of acetone.

Investigations

Investigations showed marked hypokalaemia (serum sodium 150, potassium 2.3, chloride 99 mEq/l.). The salivary potassium concentration was 23 and sodium 5.6 mEq/l., giving a Na/K ratio of 0.24. The blood sugar was 316 mg. per 100 ml. 1½ hours after a meal, and a glucose-tolerance test showed a fasting level of 166 mg. per 100 ml., rising in 1½ hours to 253 mg. and falling in 2½ hours to 205 mg. per 100 ml.; all specimens of urine contained sugar. Urinary 17-ketosteroid excretion was 60.2 mg. and 17-ketogenic steroids 30.8 mg. in 24 hours. Other findings were as follows: Hb 11.2 g. per 100 ml.; M.C.V. 98 $c\mu$; M.C.H.C. 32%; white cells 7,000 per c.mm. (85% neutrophils); platelets 120,000 per c.mm.; normal bleeding and clotting times; E.S.R. 60 mm. in first hour (Westergren); blood urea 45 mg. per 100 ml. Chest radiographs initially showed only cardiac enlargement, but subsequently patchy consolidation of the left lower lobe appeared. Prednisone did not significantly reduce the daily output of 17-ketosteroids, and this feature, together with the finding of a raised β-fraction, was considered to suggest an adrenal carcinoma as the cause of her clinically diagnosed Cushing's syndrome.

Progress

Potassium chloride by mouth in increasing doses up to 10 g. daily resulted in only a slight rise in the low serum level, though never to normal, the highest being 3.5 mEq/l. Glycosuria was controlled by soluble insulin, the daily requirement ranging between 20 and 60 units. Penicillin was given for the apparent infection in the left lower lobe of the lung, which was associated with a low-grade fever, and the signs improved, though not completely. Three weeks after admission there was an episode of right-sided colic associated with the passage of blood-clots in the urine. A hard, fixed mass was felt deep in the right loin, and a hard mass arising out of the pelvis. Hirsuties became more marked, extensive fresh purpura developed, the platelet count decreased progressively to 35,800 per c.mm. four weeks after admission, and the haemoglobin fell to 8.5 g. per 100 ml. Blood transfusion was refused.

She was transferred to Hillingdon Hospital on November 22, a month after her original admission, for further investigations with a view to adrenalectomy. Coarse crepitations were still present over the left lower lobe, where the percussion note was moderately impaired and breath sounds were diminished. Investigations confirmed the persistent hypokalaemia (3.5 mEq/l.), not associated, however, with alkalosis (serum bicarbonate 25 mEq/l.). For the first time some myelocytes were seen in the peripheral blood. The urine grew a *Proteus* on culture. Shortly after transfer her temperature and pulse rate rose rapidly and her general condition deteriorated. A blood-stream infection was suspected and subsequently confirmed, a *Proteus* being grown. Tetracycline, penicillin and streptomycin, and erythromycin were variously given without avail and she died on November 28, 1959.

Necropsy Findings

The relevant findings were as follows. About 300 ml. of blood-stained fluid was found in the left pleural cavity. There was an infiltrating white tumour 3×2×2 cm. arising in the left lower-lobe bronchus and extending up into the wall of the main bronchus. The left lower lobe was collapsed. There were several small secondary deposits in the right lung, one in the upper lobe being associated with an infarct. Hilar, mediastinal, and both groups of deep cervical lymph nodes were enlarged and invaded. The liver was studded with small secondary deposits up to 2 cm. in diameter, and there were a few minute subcapsular secondary deposits in both kidneys. The uterus was grossly enlarged (12×8×8 cm.) by secondary tumour, and also contained two degenerate fibroids up to 5 cm. in diameter and an endometrial polypus. The left lobe of the thyroid gland contained two small deposits. The bodies of all the lumbar vertebrae were riddled with tumour deposits. The suprarenals were grossly enlarged, the left measuring 8×3.5×2 cm. and weighing 25 g., and the right measuring 7×3.5×2 cm. and weighing 22 g. The enlargement was due to bilateral cortical hyperplasia, each cortex having a mottled brownish-yellow colour. On the left side there were also three tiny "pin-head" secondary deposits. The pituitary was grossly normal except for a tiny secondary deposit in the posterior lobe adjacent to the anterior lobe. The left ventricle was moderately hypertrophied. Severe bilateral haemorrhagic pyelitis and slight acute cystitis were present; the ureters were only slightly dilated. The spleen was slightly enlarged and very congested and oedematous.

Histology

The tumour arising from the left lower-lobe bronchus was an oat-cell carcinoma. Secondary carcinoma was confirmed in liver, thyroid, uterus, and a vertebra, in which reactive hyperplasia of haemopoietic tissue was noted. Microscopical examination of the suprarenals showed marked hyperplasia of the zona fasciculata of the cortex, many cells being laden with lipoid, and in addition there was one gross and several small foci of secondary carcinoma. In the pituitary there were extensive hyalinization of the basophil cells and secondary carcinoma in the boundary zone of the posterior lobe.

Case 2

A 52-year-old married woman was admitted to the Whittington Hospital on April 11, 1960, with a four-weeks history of polyuria, polydipsia, and nocturnal frequency. During this time she had also noticed pain and weakness of the right arm and leg, together with slight pain in the left leg. Ten years previously she had had a hysterectomy for uterine prolapse, but had otherwise been in good health. Her son had died of leukaemia at the age of 28. There was no family history of diabetes mellitus.

On admission she was observed to be obese and kyphotic, weighing 168 lb. (76.2 kg.) and 5 ft. (1.5 m.) tall. There were many pale abdominal striae and she had much hair on the upper lip. Her blood-pressure was 190/100 mm. Hg. There was no papilloedema, and the retinal vessels were normal. She had a systolic murmur at the apex, conducted into the neck. In the right arm there was marked weakness of the triceps and wrist and finger extensors, moderate weakness of the biceps, and slight weakness of the finger flexors, together with an absent triceps jerk. In the right leg there was slight weakness of the dorsiflexors of the foot. There was a moderate degree of wasting in the affected muscles. There was no sensory loss.

Investigations

The haemoglobin was 11.5 g. per 100 ml. and E.S.R. 19 mm. in the first hour (Westergren). Chest radiographs revealed a mass at the left upper hilum with a raised left diaphragm. There was marked glycosuria, and a glucose-tolerance test showed a diabetic-type curve, rising from a fasting level of 284 mg. per 100 ml. to a level of 375 mg. per 100 ml. at three hours. There was little ketosis, but all specimens of urine contained sugar. Serum sodium was 144 mEq/l., and the lowest recorded potassium was 3.6 mEq/l. The serum bicarbonate was normal. The 24-hour urinary 17-hydroxycorticosteroid excretion was 64 mg., 90 mg., and 72 mg. on three separate occasions, and 17-ketosteroid excretion per 24 hours was 34 mg. There was no appreciable suppression of 17-hydroxycorticosteroid output in the urine after prednisolone, 5 mg. 6-hourly, was given for 24 hours. The urinary 24-hour calcium excretion was 100 mg.; serum calcium was 10.2 mg. and serum inorganic phosphorus 2.5 mg. per 100 ml. Her 24-hour urinary creatine excretion was 400 mg. and 220 mg. on two separate occasions, and urinary creatinine excretion on the same occasions was 800 mg. and 540 mg. respectively. The serum glutamic oxalacetic transaminase was normal. Her cerebrospinal fluid was normal, under a pressure of 300 mm. of water. A radiograph of the cervical spine showed diminution of the disk spaces between C4–5 and C5–6 vertebrae. Radiographs of the lumbar spine showed considerable osteoporosis. An intravenous pyelogram showed the right kidney to be low and rotated, with a large soft-tissue shadow above it.

Progress

The diabetes was controlled with a mixture of soluble insulin 30 units and protamine-zinc insulin 15 units daily. On bronchoscopy the left upper-lobe bronchus was seen to be almost completely occluded by pressure from without. A biopsy was negative for carcinoma cells, as were three specimens of sputum. Three weeks after admission she developed pain and weakness in the left arm, and a small nodule appeared in the region of the umbilicus. This was excised, and histological examination showed it to be composed of cells typical of an oat-cell carcinoma. The abdominal striae became purple. She went downhill rapidly, developed ascites, and died of peritonitis on June 13, 1960.

Necropsy Findings

Necropsy was performed on the morning she died. A carcinoma was found arising from the bronchus of the upper lobe of the left lung with secondary growth involving the hilar lymph nodes in a mass 9 cm. across. Some growth was surrounding the left pulmonary artery, causing stenosis. There was congestion and oedema of both lungs. Carcinoma also involved the pericardium and the base of the heart. There was moderate hypertrophy of the left ventricle, with some atheroma of the coronary arteries. The left pleural cavity contained 200 ml. of clear fluid. In the abdomen there was a generalized fibrino-purulent peritonitis, with a litre of purulent fluid. Carcinomatous growth was observed in the liver and in the upper abdominal and aortic lymph nodes. The pancreas was involved with secondary growth, and showed changes of chronic pancreatitis with fat necrosis. The posterior abdominal wall was also extensively infiltrated, as was the perinephric fat surrounding the left kidney. There was growth in the cortex of this kidney and in the bladder wall. Both adrenal glands appeared to be largely replaced by carcinomatous tissue. The brain, hypothalamus, spinal cord and pituitary appeared normal. The spleen was congested. The ovaries were atrophic.

Histology (Dr. Stansfeld)

Sections of the lung tumour showed a highly cellular malignant epithelial growth, the morphological features of which suggested a poorly differentiated primary adenocarcinoma of bronchial origin. A similar type of structure was seen in metastatic tumours in the liver, pancreas, kidney, and a lymph node. In some sites the tumour showed very little differentiation of acinar structure and the appearance approached that of an undifferentiated "oat-cell" carcinoma.

Sections of a tumour present in one suprarenal gland showed clearly that metastatic carcinoma of the same type

as the lung tumour was present in a pre-existing cortical adenoma of the suprarenal. In spite of existing extensive destruction of one pole of the suprarenal tumour by secondary carcinoma, there was still a large amount of the cortical adenoma remaining.

In the light of these findings it seems highly probable that the features of Cushing's syndrome noted in this case were the result of the primary cortical adenoma of the suprarenal, and were not attributable to the bronchial carcinoma. Sections of both ovaries, pituitary, midbrain, spinal cord, and brachial plexus showed no significant changes.

Comment

Case 1

The presenting symptom in this case was a florid psychosis, and the diagnosis of Cushing's syndrome was made on the finding of trunk obesity, plethora, purple striae, increased pigmentation, hypertension, and glycosuria. Though the patient did not complain of muscle weakness, hypokalaemia was profound and resistant to relatively large amounts of potassium by mouth (up to 134 mEq daily). Urinary aldosterone estimations were not carried out ; an isolated salivary Na/K ratio was low at 0.24, but as the normal range is wide this is uncertain evidence for excess aldosterone excretion. Edmunds *et al.* (1958) record a case of Cushing's syndrome in which the average salivary Na/K ratio was 0.27, rising after partial adrenalectomy to 0.35. In Bagshawe's review (1960a) of patients with frank Cushing's syndrome showing this order of hypokalaemia none had adrenal metastases (other than those with a primary adrenal carcinoma) and one had a pituitary metastasis. Both of our cases had adrenal metastases, and Case 1 had a metastasis in the pituitary as well as adrenocortical hyperplasia.

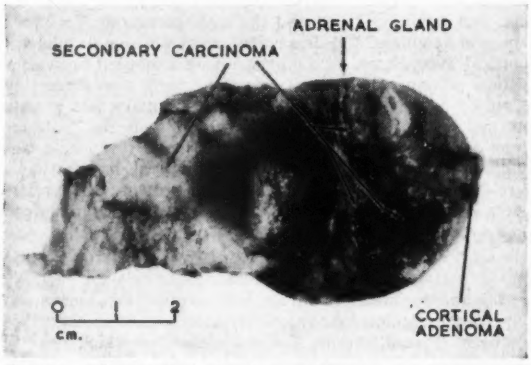
During life, however, the first suspicion of malignancy was aroused by the discovery that the purpura, not in itself unusual for Cushing's syndrome, was due to thrombocytopenia. The high urinary steroid excretion, raised β-fraction, and failure of prednisone to suppress 17-ketogenic steroid output seemed to lend further support to the diagnosis of a primary adrenal carcinoma, perhaps metastasizing widely, though in fact very high urinary steroid excretion can occur in benign tumours and even cortical hypertrophy, and suppression by prednisone can be reliably diagnosed only if urinary cortisol is estimated (Cope and Black, 1959).

Case 2

This case is of interest because of the presenting symptom of asymmetrical muscular weakness. This had been present for a month before admission—as long as the total length of the history—and predominantly involved the righ arm, and to a less extent the right leg, without sensory loss. Later the left arm was affected, though never to such an extent as the right. Examination of radiographs of the cervical spine revealed no evidence of metastatic spread from the bronchial carcinoma. Subsequently at necropsy, though the brachial plexus and spinal cord were carefully dissected out, no metastases were discovered involving either. No cerebral secondary growths were seen. In view of the presence of a bronchial carcinoma a peripheral neuropathy of the purely motor type was naturally suspected (Brain and Henson, 1958). It is unusual, however, for it to be so asymmetrical, and the cerebrospinal-fluid protein in these cases is frequently raised, though it was not in this case. The serum potassium in this case was not so low as in Case 1. The calcium excretion is sometimes raised in Cushing's syndrome (Albright, 1938), but we found no evidence of this in this case.

Discussion

As Allott and Skelton (1960) report in their review of the literature, 36 cases have been previously reported in which a non-endocrine malignant tumour (by which they mean a tumour arising in organs other than the pituitary, adrenal, or ovary) has been associated with hyperactivity of the adrenal cortex. They add two further cases, and Bagshawe (1960a) a third. To these may be added the case of Parrish (1960), where this overactivity was associated with a primary neuroblastoma arising from the sympathetic chain at the thoracic inlet, and the case of Farrant and Insley (1960),



Case 2. Adrenal gland showing carcinomatous metastases and small cortical adenoma.

where the malignant tumour was an islet-cell carcinoma of the pancreas. We add a further two cases, making 43 in all. Of these, 19 (44.2%) are in females and 22 (53.5%) in males, and in one the sex is unknown. This is a high incidence of female involvement, as Allott and Skelton point out, especially as five of seven cases of carcinoma of the pancreas were in women, and of 21 cases of carcinoma of the bronchus (including our two) eight were in women. The previously reported cases tended to occur at a younger age than is usual for that type of carcinoma, and our two patients were rather young.

In cases previously reported the rapidity of onset of symptoms of adrenal overactivity has been a characteristic feature, and the two cases we describe are no exception. Obesity, gain in weight, hypertension, thirst, polyuria, and hirsuties have been previously reported (Allott and Skelton, 1960) as notable features. Our two cases show most of these, though neither was very hypertensive. Others have been reported as showing marked muscular weakness (Bagshawe, 1960b), relieved by increased potassium intake, but none so far as having the marked, asymmetrical neuromyopathy shown by our Case 2.

Great emphasis has been placed on the hypokalaemia and metabolic alkalosis seen in these cases (Bagshawe, 1960a). Both our cases showed a low or low-normal potassium (2.3 mEq/l. in Case 1 and 3.6 mEq/l. in Case 2), but no significant alkalosis. Another feature of Case 2 is that a cortical adenoma was found in one adrenal gland, and a metastasis from the primary neoplasm of the bronchus was present in the adenoma

as well as in the adrenal cortex. Crooke's change was present in the basophil cells of the anterior pituitary of the first case, but not in Case 2. Certainly there was time in Case 1 for the full picture of Cushing's syndrome to develop, and it is interesting that this hyalinization of the basophil cells was so marked. In Case 2 it would appear that there was not time for this to develop. As Allott and Skelton (1960) point out, this finding has been an inconstant feature of previously reported cases; it probably takes some time to develop, and is therefore absent from those cases in which the disease is rapid in onset and progression.

At least four theories may be advanced to account for this observed association of carcinoma with adrenal overactivity. (1) It may be due entirely to chance. Against this is the observation that these cases fall into a distinct pattern, with variations from the usually observed incidence in females of the carcinomata concerned, together with an unusual age distribution. (2) The carcinoma is stimulated by adrenal overactivity. There is little evidence that this should be so. Though the experimental evidence of Pomeroy (1954) in mice supports this theory, neither Kaliss *et al.* (1954) nor Fisher and Fisher (1959) were able to find experimental support for this in rats. (3) There may be stimulation by the cancer of the adrenal glands or adrenal cortical adenomata to hyperactivity. It is tempting to suggest that this may have happened in Case 2, where metastatic carcinomatous growth occurred in an adrenal cortical adenoma. Such adenomata are not uncommonly seen at necropsy in patients not suspected clinically of having Cushing's syndrome, and are presumably often, therefore, non-active. (4) Representatives of any or all of the above explanations may be found in any series of patients showing this association. Though increased aldosterone production has been postulated as a possible explanation of the findings of this association (Spaulding *et al.*, 1955), only one case has so far been reported where this has been found to be so (Webster *et al.*, 1959). Conceivably Case 1 could be explained on this basis on the somewhat tenuous evidence of the low Na/K ratio, but this is doubtful, to say the least of it.

We are no nearer to explaining the mystery of why hypokalaemic Cushing's syndrome should occur in association with malignant disease involving such widely separated organs as the thymus (Duguid and Kennedy, 1930), colon (Warren, 1945), bronchus (Brown, 1928), and prostate (Webster *et al.*, 1959). We feel, however, that it is important to go on reporting these cases as they occur, since by comparing their similarities and differences a common factor may emerge to explain this syndrome.

Summary

Two cases in which carcinoma of the bronchus was associated with Cushing's syndrome are reported. They are compared with similar cases in the literature where this association between malignant disease and adrenal overactivity has been observed. These two cases are of interest because one presented with a florid psychosis and purpura, which proved to be due to bone-marrow metastases, and the other with an asymmetrical neuromyopathy. Various theories are advanced in an endeavour to explain this association.

We thank Dr. M. G. Ashby and Dr. E. Idris Jones for permission to publish information about their patients; also Dr. A. G. Stansfeld, of St. Bartholomew's Hospital, for the histological report and photographs of Case 2, and Dr. Jones-Williams, of Mount Vernon Hospital, for the α- and β-fraction estimations on Case I. Thanks are also due to Dr. J. D. O'D. Lavertine for the post-mortem report on Case 1, and Mr. Macdonald for the photographs of this case, taken at Harefield Hospital.

REFERENCES

Albright, F. (1938). *N. Engl. J. Med.*, **218**, 813.
Allott, E. N., and Skelton, M. O. (1960). *Lancet*, **2**, 278.
Bagshawe, K. D. (1960a). Ibid., **2**, 284.
—— (1960b). Ibid., **2**, 287.
Brain, W. R., and Henson, R. A. (1958). Ibid., **2**, 971.
Brown, W. H (1928). Ibid., **2**, 1022.
Cope, C. L., and Black, E. G. (1959). *Brit. med. J.*, **2**, 1117.
Duguid, J. B., and Kennedy, A. M. (1930). *J. Path. Bact.*, **33**, 93.
Edmunds, A. W. B., McKeown, K. C., and Coleman, P. N. (1958). *J. clin. Path.*, **11**, 237.
Farrant, P. C., and Insley, J. (1960). *Lancet*, **2**, 434.
Fisher, T. N., and Fisher, E., jun. (1959). *Proc. Soc. exp. Biol. (N.Y.)*, **100**, 780.
Kaliss, N., Borges, P. R. F., and Day, E. D. (1954). *Cancer Res.*, **14**, 210.
Parrish, J. A. (1960). *Lancet*, **2**, 603.
Pomeroy, T. C. (1954). *Cancer Res.*, **14**, 201.
Spaulding, W. B., Oille, W. A., and Gornall, A. G. (1955). *Ann. intern. Med.*, **42**, 444.
Warren, F. L. (1945). *Cancer Res.*, **5**, 49.
Webster, G. D., jun., Touchstone, J. C., and Suzuki, M. (1959). *J. clin. Endocr.*, **19**, 967.

ACUTE CARBON TETRACHLORIDE POISONING

TRANSAMINASE AND BIOPSY STUDIES

BY

J. K. DAWBORN, M.B., B.S., M.R.A.C.P.
Drug Houses of Australia Research Fellow

MARY RALSTON, M.B., B.S., D.C.P., M.C.P.A.
Pathologist to the Clinical Research Unit

AND

S. WEIDEN, M.Sc., Ph.D.
Biochemist to the Clinical Research Unit

From the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital

[WITH SPECIAL PLATE]

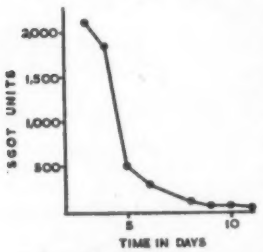
Many features of acute carbon tetrachloride poisoning are well established (Cameron and Karunaratne, 1936; Council on Industrial Health, 1946; Hardin, 1954). However, the following case of carbon tetrachloride poisoning provided a unique opportunity for studying the course of hepatic damage by means of serial estimations of the serum glutamic oxalacetic transaminase (S.G.O.T.) level (method of Reitman and Frankel, 1957) and serial liver biopsies.

Case Report

A storeman aged 22 years accidentally swallowed a mouthful of carbon tetrachloride. Immediately his head began to throb, he felt faint, and two hours later he vomited and passed dark urine. The following day he suffered increasing anorexia and abdominal pain. On the third day he was admitted to hospital, and clinical examination disclosed pronounced tenderness and rigidity in the epigastrium. The urine contained granular casts, and there was moderate proteinuria but no bilirubinuria. The initial biochemical analyses were as follows: serum bilirubin 1.4 mg. per 100 ml.; serum albumin 2.7 g. and globulin 2.3 g.

per 100 ml.; S.G.O.T. 2,120 units; serum alkaline phosphatase 13 King–Armstrong units; cephalin flocculation + + +; prothrombin index 19% of normal; serum vitamin B_{12} 1,000 $\mu\mu$g. per ml.; serum amylase 266 units; urinary diastase 80 units; and blood urea 27 mg. per 100 ml.

Treatment consisted in a full diet, with administration of choline hydrochloride, 3.0 g. daily, antihistamine ("benadryl"), 200 mg. daily, nicotinic acid, 400 mg. daily, and vitamin K. On the fifth day he felt well and was no longer tender in the epigastrium; the S.G.O.T. level had fallen from 2,120 to 520 units and continued to fall (see Graph). On the ninth day "bromsulphalein" retention was 38%, serum amylase less than 100 units, and urinary diastase 20 units. All other biochemical tests gave normal findings. The prothrombin index was 100%.



Graph showing transaminase (S.G.O.T.) levels in moderately severe carbon tetrachloride poisoning during phase of recovery. There was a striking fall in level corresponding with clinical improvement. First estimation on third day probably did not represent highest level reached.

Liver biopsy on the ninth day revealed centrilobular zonal necrosis of one-third to one-half of each liver lobule (Special Plate, Fig. 1). In these areas there was an inflammatory infiltrate of lymphocytes, plasma cells, and macrophages containing bile pigment. Scattered surviving liver cells were present near the central vein. The reticulin framework was preserved (Special Plate, Fig. 2). Renal biopsy (tenth day) showed only pigment in the epithelium of occasional medullary tubules. Gastric biopsy (eleventh day) was normal.

By the twenty-eighth day liver biopsy revealed considerable improvement. There were still centrilobular damage and fatty change, but liver-cell regeneration was present (Special Plate, Fig. 3). In a third liver biopsy, obtained on the seventieth day, there was almost complete restoration to normal; only a few inflammatory cells remained in the sinusoids and some fatty change persisted.

Discussion

Carbon tetrachloride causes swelling of mitochondria in liver cells and increased permeability of the mitochondrial membrane. There are disorganization of enzyme activity and loss of co-factors and enzymes from the mitochondria (Christie and Judah, 1954; Gallagher *et al.*, 1956). Choline and antihistamines, which lessen this damage to mitochondria (Christie and Judah, 1954; Judah and Rees, 1959; Judah, 1960), appeared to be effective in our case.

Raised levels of S.G.O.T. in carbon tetrachloride poisoning have been reported in human beings and in animals (Wróblewski *et al.*, 1956; Block and Cornish, 1958). In animal experiments S.G.O.T. was the most sensitive of the three enzymes measured, and the rise in S.G.O.T. was proportional to the extent of liver damage. In a study at the Royal Melbourne Hospital of 48 patients with various forms of liver disease (O'Brien *et al.*, 1960) there was an approximate correlation between S.G.O.T. levels and the extent of liver-cell necrosis. In the present case an S.G.O.T. of at least 2,120 units was associated with necrosis of one-third to one-half of every liver lobule in the biopsy. The prompt fall in S.G.O.T. level was associated with liver-cell regeneration after cessation of injury. The administration of choline and antihistamines may have contributed to this fall by lessening release of enzymes from the liver cells.

The liver histology was consistent with previously described changes (Himsworth, 1950). The reticulin framework remained intact despite extensive centrilobular necrosis, so that full recovery could be anticipated (Special Plate, Fig. 2). Damage to the kidney was slight, as is usually the case when poisoning follows ingestion of carbon tetrachloride.

The present case illustrates the value of serial S.G.O.T. estimations in assessing the extent and duration of liver damage and the rate of recovery in carbon tetrachloride poisoning. There was a rapid and extensive cell necrosis which was demonstrated by liver biopsy to involve approximately half the liver lobule.

Summary

A non-fatal case of carbon tetrachloride poisoning is reported. S.G.O.T. levels and liver histology were followed at intervals for up to 70 days. The former returned to near normal after nine days, while the latter was still abnormal at 28 days. Clinical recovery was complete by 10 days and histological recovery by 70 days. The results are discussed.

We wish to thank Professor G. S. Christie for his advice in the clinical management of this case, and Dr. I. J. Wood for permission to report it. The illustrations were prepared by Mr. E. Matthaei, of the University of Melbourne.

References

Block, W. D., and Cornish, H. H. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **97**, 178.
Cameron, G. R., and Karunaratne, W. A. E. (1936). *J. Path. Bact.*, **42**, 1.
Christie, G. S., and Judah, J. D. (1954). *Proc. roy. Soc. B*, **142**, 241.
Council on Industrial Health (1946). *J. Amer. med. Ass.*, **132**, 786.
Gallagher, C. H., Gupta, D. N., Judah, J. D., and Rees, K. R. (1956). *J. Path. Bact.*, **72**, 193.
Hardin, B. L., jun. (1954). *Industr. Med. Surg.*, **23**, 93.
Himsworth, H. P. (1950). *Lectures on the Liver and its Diseases*, 2nd ed. Blackwell, Oxford.
Judah, J. D. (1960). *Nature (Lond.)*, **185**, 390.
—— and Rees, K. R. (1959). *Biochemical Society Symposia*, No. 16, p. 94.
O'Brien, E. N., Paterson, B., Ralston, M., and Mackay, I. R. (1960). *Aust. Ann. Med.*, **9**, 295.
Reitman, S., and Frankel, S. (1957). *Amer. J. clin. Path.*, **28**, 56.
Wroblewski, F., Jervis, G., and LaDue, J. S. (1956). *Ann. intern. Med.*, **45**, 782.

The formation of a medical faculty of Auckland University as a further step in the establishment of a medical school has been announced by the university council. The following were constituted the faculty: the professor and other full-time members of the Postgraduate School of Obstetrics and Gynaecology; Professor H. M. CAREY, Associate-professor G. H. GREEN, and one other to be appointed; the sub-dean of the branch medical faculty of the University of Otago, Dr. W. E. HENLY; three full-time tutors in medicine, surgery, and paediatrics at Auckland Hospital, Dr. H. K. IBBERTSON, Dr. J. C. GILLMAN, and Dr. R. H. CAUGHEY; the physician-in-charge of the medical unit at Auckland Hospital, Dr. J. D. K. NORTH; three members of the postgraduate committee of medical education in Auckland, to be appointed; three professors from the departments of chemistry, physics, and zoology, to be appointed; and the dean of the science faculty, Professor F. H. SEGAR.

Preliminary Communications

Adenovirus and Intussusception

The aetiology of intussusception in children has remained obscure, although the development of this abnormality in adult cases has often been attributed to the presence of a tumour or some similar focus. The commonest location of the lesion in intussusception is the small intestine, in the region of the ileocaecal valve, where the heaviest concentration of lymphoid tissue is to be found.

In children, intussusception has been attributed to imbalance of intestinal muscular contraction, to the presence of lymphoid tissue about the ileum, and to varying directions of peristaltic waves in this region (Anderson, 1957).

It has been known for some time that adenoviruses may be excreted in large quantities in the stool (Kjellén *et al.*, 1957; Gardner *et al.*, 1960; Duncan and Hutchinson, 1961) and for long periods of time (Gardner *et al.*, 1961). With current methods of isolation it would appear unlikely that adenovirus could be isolated so easily from the stool over long periods of time if the presence of virus was solely the result of passive swallowing from the upper respiratory tract. If this view is accepted it would appear that adenoviruses must multiply somewhere in the intestinal tract. With these observations in mind, it was decided to examine the stools of all confirmed cases of intussusception in children seen during a period of about a year. Over the same period the first specimen of faeces of all admissions was examined for viruses, and children in the equivalent age-groups whose clinical condition was unlikely to be of a viral nature were selected to act as controls. The results of the investigation, presented below, substantiate the simultaneous observations of Graham Ross and Potter (1961).

MATERIALS AND METHODS

Faeces from 10 cases of intussusception, taken as soon as possible after operation, were examined on HeLa cells, and 13 ward controls between the ages of 3 months and 1 year were similarly examined. The ward patients were those who had been admitted on account of trauma or for the treatment of a congenital hernia. Cases which might have a possible virus aetiology were excluded. Ten per cent. faeces suspension in 0.2-ml. and 0.1-ml. quantities were inoculated into HeLa cell tubes and maintained for a minimum of 28 days. It was necessary occasionally to passage agents during the 28 days for non-specific changes. Likely degenerating agents were passaged and if still present were subjected to a complement-fixation test using a standard adenovirus serum. If the result of this test was positive a neutralization test was performed, using the appropriate antisera. The methods employed were similar to those described by Munro-Ashman *et al.* (1958).

If an agent did not give a positive complement-fixation test with adenovirus antisera, neutralization with a rabbit herpes simplex antiserum was attempted, followed by inoculation on to the chorio-allantoic membrane of 10–12-day-old fertile hens' eggs.

Monkey-kidney tubes were inoculated when available, and 7 out of the 10 cases of intussusception and 5 out of the 13 controls were thus examined.

RESULTS

Of the 10 cases of intussusception examined (seven males and three females), all were under 1 year except one girl aged 2¼ years. The results are shown in the Table.

Analysis of Cases of Intussusception

Case No.	Sex	Age	Adenovirus	Other Viruses
1	F	2¼ years	–	–
2	M	8 months	–	–
3	M	10 ,,	–	–
4	M	5 ,,	–	Herpes simplex
5	M	5 ,,	+	–
6	M	5 ,,	+	–
7	F	9 ,,	+	–
8	M	6 ,,	+	–
9	F	6 ,,	+	–
10	M	4 ,,	+	–

In three cases no viruses were isolated in HeLa cells. From the remaining seven, six stools yielded adenovirus, while the seventh yielded herpes simplex. Four of the adenoviruses were type 5, one was type 4, and one was type 7. None of the 13 control infants had any viruses in their stools as detected by HeLa cells. In none of the faeces examined in this investigation were any enteroviruses detected either on HeLa cells or monkey-kidney cells when used. In two cases adenoviruses were isolated on both monkey-kidney and HeLa cells.

As this was by way of an exploratory investigation no blood specimens were taken from this young age-group, nor were follow-up faeces, except in one case (No. 10) in which the same adenovirus type 5 was being excreted two months later.

DISCUSSION

Though the figures were small the results indicate that virus was being excreted in large quantity in the faeces of 70% of cases of intussusception, 60% being adenovirus. Three of the cases gave a history of upper respiratory infection, which may have been the source of their infection. However, the experience gained in the study of adenovirus excretion in a closed community (Gardner *et al.*, 1961) showed that adenovirus, particularly type 5, could be excreted for a long time without apparent ill-health. This may be of interest, as four of the six adenoviruses isolated were types associated with long-term faecal excretion. The possibility exists that the adenoviruses multiply in the lymphoid tissue of the bowel, perhaps in the Peyer patches and the terminal ileum, and result in the enlargement of this tissue. This factor, either alone or in association with physiological upset due to a change to mixed feeding or some dietary indiscretion, may lead to the start of an intussusception. Abdominal symptoms are certainly not uncommon in adenovirus infections (Gardner *et al.*, 1960), and they have been found in the mesenteric glands (Kjellén *et al.*, 1957).

It must be emphasized that this is a preliminary report and adequate confirmation of these results is necessary. One could speculate that intussusception was just one of the rarer manifestations of adenovirus infections of the bowel in the young, while many more children of this age-group may present with diarrhoea and perhaps in the older child as mesenteric adenitis. Suitable cases at operation should be examined and compared with normal children and children with diarrhoea, mesenteric adenitis, and perhaps acute appendicitis, before a clearer picture emerges of the part played by adenoviruses in the aetiology of intussusception and other bowel diseases.

SUMMARY

Ten cases of intussusception are reported. An adenovirus was isolated from the faeces of six of these patients and herpes simplex from the faeces of one. Thirteen subjects of a similar age examined as controls were negative. The possible role of adenovirus in the aetiology of intussusception is discussed.

I am indebted to the Child Health Department, Newcastle upon Tyne, and the clinicians at Sheriff Hill Hospital, Gateshead, from whom specimens were obtained.

ADDENDUM.—Since this investigation was completed three further cases of intussusception have been examined; two were associated with adenovirus excretion.

P. S. GARDNER, M.D., Dip.Bact.,
Consultant Virologist, United Hospitals and King's College, Newcastle upon Tyne.

REFERENCES

Anderson, W. A. D. (1957). *Pathology*. Kimpton, London.
Duncan, I. B. R., and Hutchinson, J. G. P. (1961). *Lancet*, **1**, 530.
Gardner, P. S., McGregor, C. B., and Dick, K. (1960). *Brit. med. J.*, **1**, 91.
—— Wright, A. E., and Hale, J. H. (1961). Ibid., **2**, 424.
Kjellén, L., Sterner, G., and Svedmyr, A. (1957). *Acta paediat. (Uppsala)*, **46**, 164.
Munro-Ashman, D., Gardner, P. S., Taylor, C. E. D., and McDonald, J. C. (1958). *Lancet*, **2**, 121.
Ross, J. G., and Potter, C. W. (1961). Ibid., **1**, 81.

Medical Memoranda

Case of Mesenteric Reticulosarcoma Associated with Gluten-sensitive Steatorrhoea

[WITH SPECIAL PLATE]

Several authorities have recently demonstrated that the majority of cases of idiopathic steatorrhoea, or adult coeliac disease, will respond to a gluten-free diet. In fact Cooke (1958) states: "From reports in the literature and from personal experience it does seem justifiable to assume, should clinical cure result, that the patient was suffering from adult coeliac disease."

The patient concerned in this report suffered a severe degree of steatorrhoea and died of mesenteric reticulosarcoma. For 18 months there was a complete response to a gluten-free diet.

CASE HISTORY

The patient first sought advice in October, 1955, when aged 49. Previously his health had been good and he had led a normal, active life. He gave a history of loss of weight (at least 28 lb.—12.7 kg.), anorexia, fatigue, and sore tongue for the previous year. The stools had become unusually bulky and occasional nausea and vomiting occurred.

Examination revealed a tall man of normal skeletal proportions. There was evidence of recent loss of weight and pallor. The abdomen was mildly distended; there were no other abnormal physical signs.

Investigations gave the following results:—Blood count: Hb 9.8 g. per 100 ml.; packed cell volume 27%; W.B.C. 3,800 per c.mm., normal differential. Sternal marrow biopsy: megaloblastic. Barium meal: normal, rapid passage of barium into large intestine. Gastric secretion: free acid present. Oral glucose-tolerance test: very flat curve, fasting blood sugar 67 mg. per 100 ml. Stool occult blood: absent.

Since there was no response to injections of vitamin B_{12}, folic acid was given for the anaemia and full metabolic studies for calcium, phosphorus, and nitrogen were begun (see Graph). On a daily fat intake of 75 g., 20 g. per day appeared in the faeces, thus confirming the diagnosis of steatorrhoea. Urine calcium was 150 mg. per day, but faecal calcium exceeded the intake so that a strongly negative balance resulted. A gluten-free diet was tried (Period 4). There was only a slight reduction in faecal fat and calcium—not enough to justify continuation of such a complicated regimen—and a low-fat diet was given (Period 11). Weight increased and anaemia diminished. The patient left hospital in March, 1956 (corresponding to Period 16), three months after admission, and attended as an outpatient. This improvement did not support an earlier suggestion of malignancy.

However, he failed to regain perfect health, and a gluten-free diet was reintroduced in July, 1956. In January, 1957, the haemoglobin had risen to 13.7 g. per 100 ml., normal weight had been regained, and the patient felt well. In view of the biochemical interest of the case he was admitted for further metabolic studies in February, 1957. There was considerable improvement in the balance. After only six days on a normal diet containing gluten the patient felt ill, with nausea, stomatitis, abdominal pain, and bulky, offensive stools. A return to a gluten-free diet became essential (Period 21). Stool fat rose for several periods, reaching a maximum of 27 g. per day. There was an associated rise in faecal calcium, making the balance negative again. Improvement followed resumption of the gluten-free diet (Periods 24 and 25). Streptomycin was given at this time, but its effect was equivocal.

By July, 1957, three months after returning to a gluten-free diet, normal health was regained. Later in the year the patient reported a small loss of weight and fever, and he was readmitted to hospital in January, 1958. The fever was persistent, remaining between 101° and 104° F. (38.3° and 40° C.) for four or five days at a time and then falling to 99° F. (37.2° C.) for two or three days. Three weeks later the tip of the spleen became palpable. The haemoglobin fell to 8.8 g. per 100 ml.; white cell count 4,000 per c.mm. with a normal differential. Investigations to establish a cause for the fever (stool and blood culture, serum agglutination, barium studies, intravenous pyelography, etc.) were negative. Oral glucose tolerance was normal. Plasma proteins totalled 5.5 g. per 100 ml. (albumin 2.9 g., globulin 2.6 g.). Electrophoresis showed decreased albumin with increased α-globulins. Mantoux-testing was negative at 1:100 old tuoerculin and a chest radiograph was normal. At this stage the stools were normal in consistency and the fat content was only 22 g. per 100 g. dried weight. The effect of intramuscular penicillin was equivocal in that he became afebrile for a few days, but this was not sustained.

Laparotomy was performed and showed splenomegaly, small, firm peripheral mesenteric lymph nodes, and a mass of enlarged nodes at the root of the mesentery. Dr. C. F. Ross reported on the biopsy specimens as follows: "Liver: mild passive congestion only. Peripheral mesenteric node: old inflammatory change and fibrosis only. Lymph node from root of mesentery: normal structure replaced by mass of reticulum cells with much necrosis (Special Plate, Fig. 1). Reticulin impregnation shows marked network throughout the gland (Special Plate, Fig. 2). No Schiff-positive macrophages present. The appearances are those of reticulosarcoma."

Following laparotomy the patient's condition deteriorated and he died three weeks later after transfer to another hospital for radiotherapy. Unfortunately necropsy was not performed.

DISCUSSION

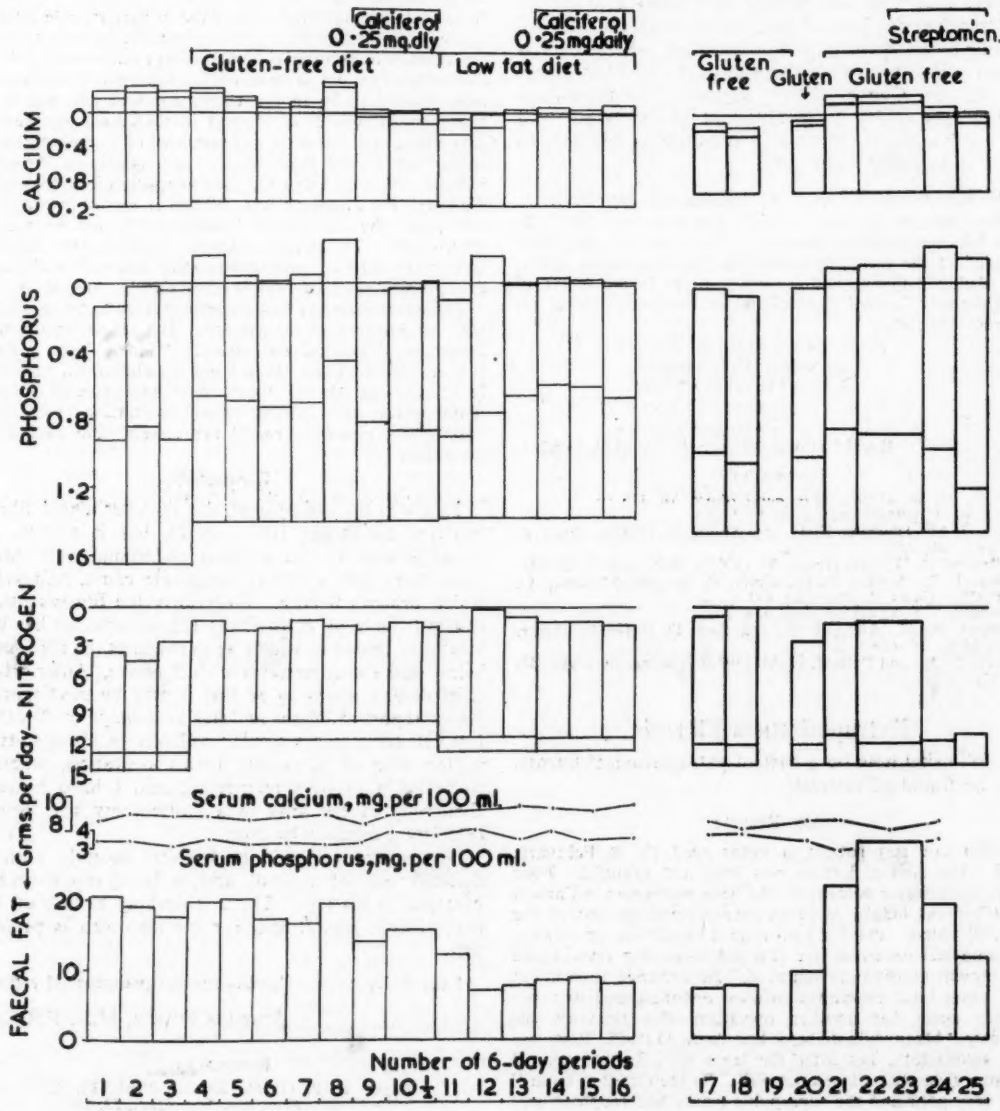
It is possible that this case represents a random association between idiopathic steatorrhoea and reticulosarcoma, or mesenteric reticulosarcoma complicating a case of occult idiopathic steatorrhoea and rendering it overt. However, mesenteric lymphoma, including reticulosarcoma, associated with steatorrhoea is a well-recognized entity, though gluten sensitivity has not previously been noted in such cases. The later age

of onset of symptoms, associated with an eventually rapid deterioration and lymph-node involvement apparently restricted to the retroperitoneal area, makes a causal relationship between the two conditions much more likely and the gluten sensitivity a factor of considerable interest. Sleisenger *et al.* (1953) reported four personal cases of mesenteric lymphoma associated with steatorrhoea with a review of 13 other cases from the literature. More recently cases have been mentioned by Friedlander and Gorvy (1955), Upshaw and Pollard (1957), and French *et al.* (1957).

From the series where figures are given it would appear that between 5% and 10% of all adult cases of apparently idiopathic steatorrhoea will eventually be found to be secondary to lymphoma of the small bowel or mesenteric lymph nodes. The average age of onset in the lymphoma group is 50 years, some five years older than the idiopathic group, and 80% of cases have been recorded in males, whereas idiopathic steatorrhoea is more common in females. The average duration of symptoms before investigation is only seven months in the lymphoma group as opposed to 40 months for idiopathic steatorrhoea, and the average survival after investigation is only six months in the lymphoma group.

It is interesting that in a review of 14 cases of lymphoma of the small intestine by Skrimshire (1955), in all of which the local lymph nodes were enlarged at laparotomy but not necessarily involved by lymphoma microscopically, he commented that on the whole the patients were well nourished and that the only patient suspected of steatorrhoea showed a normal fat balance. The average age of Skrimshire's adult patients was 50 years, and the average survival after operation, excluding one patient with follicular lymphoma who survived six years, was seven months.

The prognosis in cases of mesenteric lymphoma after admission to hospital would therefore appear to be equally serious whether steatorrhoea is present or not. In all the cases recorded in the above five series the absence of peripheral lymphadenopathy was a striking



D

feature, and frequently the mesenteric and para-aortic nodes were the only ones involved. It has been suggested by Cooke (1958) that there is no evidence that mesenteric lymphoma can be associated with steatorrhoea unless there is involvement of the bowel wall. There was no macroscopic evidence of this in our case, and the small peripheral mesenteric lymph nodes showed fibrosis only. In the case recorded by Friedlander and Gorvy (1955) there was only one small tumour in the ileum, with marked involvement of the mesenteric, retroperitoneal, and parapancreatic nodes. It would therefore appear, as suggested by Comfort (1958), that steatorrhoea may be due to regional lymphatic obstruction.

It is apparent that six of the 17 cases recorded by Sleisenger *et al.* (1953) responded to a low-fat diet for periods up to 20 months. A gluten-free diet may take several months to produce a remission in idiopathic steatorrhoea, and, even if other patients with lymphomatous steatorrhoea might respond to this diet, it is unlikely that they will survive long enough to do so. A gluten-free diet has not yet been shown to be effective in regional enteritis, or Crohn's disease, where there is extensive involvement of the wall of the small intestine, and if, as Cooke (1958) suggests, lymphomatous steatorrhoea is due to involvement of the bowel wall and not lymphatic blockade, a response to this diet, as in our case, might occur.

We wish to thank Dr. J. R. Nassim and Dr. O. R. L. Plunkett for permission to publish this case, and Dr. C. F. Ross for the photomicrographs. The case was originally included in the series published by Nassim, Saville, Cook, and Mulligan (1959), and we are grateful to the editor of the *Quarterly Journal of Medicine* for permission to reprint the metabolic data.

C. N. BEST, M.B., M.R.C.P.Ed.,
Late Senior Medical Registrar,
St. Peter's Hospital, Chertsey.

P. B. COOK, M.D., M.R.C.P., D.P.H.,
Late Medical Registrar,
Royal National Orthopaedic Hospital, London.

REFERENCES

Comfort, M. W. (1958). *Gastroenterology*, **34**, 476.
Cooke, W. T. (1958). *Brit. med. J.*, **2**, 261.
French, J. M., Hawkins, C. F., and Smith, N. (1957). *Quart. J. Med.*, **26**, 481.
Friedlander, P. H., and Gorvy, V. (1955). *Brit. med. J.*, **2**, 809.
Nassim, J. R., Saville, P. D., Cook, P. B., and Mulligan, L. (1959). *Quart. J. Med.*, **28**, 141.
Skrimshire, J. F. P. (1955). Ibid., **24**, 203.
Sleisenger, M. H., Almy, T. P., and Barr, D. P. (1953). *Amer. J. Med.*, **15**, 666.
Upshaw, C. B., and Pollard, H. M. (1957). *Gastroenterology*, **33**, 104.

Extraperitoneal Fibrosis

The following note on a case of extraperitoneal fibrosis may be found of interest.

CASE REPORT

I first saw this patient, a sailor aged 73, in February, 1956. His clinical history was long and eventful. Four years previously a colostomy had been performed in Canada for what was judged to be an inoperable carcinoma of the sigmoid colon. On his arrival in England he attended a proctological centre, where this judgment was revised and the growth successfully removed. He returned to sea, but two years later developed urinary retention and was put ashore again for another operation—this time on his prostate. Meanwhile diabetes had declared itself. Recovery was satisfactory, but after the lapse of a further year it became clear that all was not well. By then urinary control was very poor and the suprapubic fistula had reopened and was leaking profusely. He reported to the proctological centre, where he was found to have a large mass in the lower abdomen underlying the midline scar. A diagnosis of carcinoma of the prostate with upward extension was made and he was referred to a urological centre for orchidectomy. One testicle only was removed. Discouraged, he returned to the proctological centre to seek the advice of his former surgeon, who said the only hope lay with pelvic evisceration.

When I saw him he had urethral incontinence, a leaking fistula, and a mass with well-defined margins extending from pubis to umbilicus and outwards to the left iliac fossa and left lumbar region. His condition was truly deplorable.

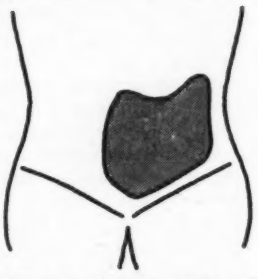


Diagram showing extent of fibrous plaque, which was 2 in. (5 cm.) in depth.

Investigation was difficult because no instrument could be passed into the bladder. It seemed, however, that part of the urinary trouble could be ascribed to some form of obstruction at the bladder neck. In the interests of cleanliness and comfort I undertook to relieve this, which I set out to do through a suprapubic incision. The mass proved to be in the abdominal wall and not in the abdomen. It was 2 in. (5 cm.) in thickness, involved the musculature far and wide, and consisted of a gristly tissue not unlike that found in the immediate neighbourhood of a suprapubic drainage-tube that has been in position for a long while. Although the approach was difficult it was easy enough to cut away the contracted bladder neck and relieve the obstruction. The patient made an uninterrupted recovery, and at the time of writing was alive and well without the mass, which resolved rapidly after this last operation.

The tissue from the bladder neck proved to be myofibrous with no evidence of malignancy. The report on the tissue from the abdominal wall stated: "Fairly large piece of rubbery fibrous tissue taken from the abdominal wall. This is collagenous fibrous tissue showing scattered areas of lymphocytes and plasma-celled infiltration with some eosinophils, especially round the vessels. No evidence of neoplasm."

COMMENT

This was an example of the retroperitoneal fibrosis reported by Raper (1956, 1960), but it affected the posterior and not the anterior abdominal wall. Moreover, there was a clearly assignable cause, removal of which brought a cure. Posteriorly the fibrosis usually causes trouble by constricting the ureters, but has been known to spread so widely as to constrict the iliac vessels below and the common bile duct above. Anteriorly its chief danger seems to be that it may be misdiagnosed. Raper reports 50 cases and has knowledge of 70 others. I myself have seen a similar collagenous fibrosis arising in the scar of a radical breast operation, where it suggested a massive recurrence, and I have heard of something of the kind in a gastrectomy scar complicated by a fistulous leakage.

My patient returned to hospital recently with his diabetes out of control and a lower-motor-neurone paralysis in his legs. There is nothing to link up with the previous operations, and his abdomen is perfectly soft.

I thank Dr. G. E. Thomas for the pathological report.

STEPHEN POWER, M.S., F.R.C.S.

REFERENCES

Raper, F. P. (1956). *Brit. J. Urol.*, **28**, 436.
—— (1960). *Proc. roy. Soc. Med.*, **53**, 690.

Reviews

THERAPEUTIC COMMUNITY

Community as Doctor. New Perspectives on a Therapeutic Community. By Robert N. Rapoport, with the collaboration of Rhona Rapoport and Irving Rosow. Introduction by Maxwell Jones, C.B.E., M.D., M.R.C.P.(Edin.), D.P.M. (Pp. 325+x. 42s.) London: Tavistock Publications. 1961.

This is a first-hand report of an organization and methods investigation into the efficiency of the Belmont Social Rehabilitation Unit. In spite of a gloss of tables and χ^2 calculations it is essentially anecdotal. However, to the present reviewer, Dr. Rapoport's descriptive analysis of the functions, problems, successes, and failures of the unit appears to reach a very high level of unbiased reporting. Nevertheless, certain aspects of the author's theoretical orientation demand comment. In the first place he apparently subscribes to an undimensional approach—people are more or less adjusted—and redefines his diagnostic categories in terms of a continuous dimension of ego-strength. It is a little difficult to see the value of this. "Ego-strength" can be little more than a summary of the overall effectiveness that an individual shows in adapting himself to society. Further, since this diagnostic system leads Dr. Rapoport to classify "effective" psychopaths with "neurotics" and "ineffective" psychopaths with "psychotics," it clearly blurs more distinctions than it creates.

The other important theoretical stand adopted by Dr. Rapoport is a sharp conceptual distinction between treatment and "rehabilitation," which incidentally he describes at one point as a therapeutic procedure. Such a distinction may be a valid one, particularly in a theoretical setting in which behavioural disturbance is seen as the psychological expression of distinct disease processes. It seems less appropriate to a conceptual formulation which sees the human situation as that of a round peg in a polygonal hole with n sides: n taking a low value for psychiatric patients—less than three for psychotics. The reviewer suspects that the author's attack on the unit's failure to distinguish between treatment and rehabilitation represents a partially covert belief that the unit's permissive milieu became at times a happy asylum for the psychopath at the expense of its function of changing the individual's personality in the direction of a greater tolerance of conventional *mores*.

An assumption which may well be the lowest common factor of the two great ideologies of our day is that the healthy man is the man who conforms with the demands of his social group. Is mental health a state in which a man functions efficiently or a state in which he functions comfortably? The answer to this question may be a value judgment, but to forget that this issue exists may prejudice progress towards either goal.

Has Dr. Maxwell Jones's experimental unit been successful? Dr. Rapoport's book begs this question, but he has made it abundantly clear that both the unit itself and his own investigation have been extremely worth while. The book is filled with postulates and falls into the medium jargon range, but its vices are as interesting as its virtues and it should certainly be read by all who are interested in techniques for changing the personalities of men and women.

ALICK ELITHORN.

PROGRESS IN VIROLOGY

Progress in Medical Virology. Edited by E. Berger and J. L. Melnick. Volume 3. (Pp. 496; illustrated. Sw. Fr. 80.) Basle and New York: S. Karger. 1961.

Progress in Medical Virology was first published in 1958 as an international series to present new facts and new techniques for the study of viruses. Virology is a rapidly growing subject with many facets—aetiology, diagnosis, epidemiology, immunization—in all of which great developments are being made. The third volume, the largest so far, consists of approximately 500 pages with eight chapters carefully selected for their topical importance. N. J. Schmidt and E. H. Lennette contribute a valuable article on serodiagnosis with up-to-date accounts of fluorescence microscopy and haemagglutination. The natural history of the arthropod-borne viruses is discussed by W. C. Reeves in a fascinating article on the over-wintering of these viruses, in which he attempts to explain some aspects of the endemic persistence of these organisms. An extensive chapter on fluorescent antigen–antibody techniques (in German) by Von G. Poetschbe is fully documented, informative, and well illustrated. H. M. Gelfand discusses the occurrence of Coxsackie and E.C.H.O. viruses in nature, a subject of growing interest in human medicine. The use of live vaccines against poliomyelitis, mumps, and measles is discussed by A. A. Smorodinksev. A useful survey on the role of viruses in the aetiology of congenital malformations is made by R. J. Blattner and F. M. Heys. The viral aetiology of leukaemia is discussed in a valuable and factual account by L. Dmochowski.

This is a most informative book in which virologists will find much to interest them. The selection of material, standard of production, and references are all excellent.

J. A. DUDGEON.

CHILD PSYCHOLOGY

Handbook of Research Methods in Child Development. Edited by Paul Henry Mussen. (Pp.1,061; illustrated. 122s.) London: John Wiley and Sons. 1961.

This is a massive, heavy volume written by a team of expert child psychologists with the aim of reviewing methods of research in child development, physical and mental. With the exception of one chapter, that written by Inhelder and Matalon, of Geneva, all the writers are American. The first four chapters are concerned with research design and the use of observation and experimental methods. The next three chapters are concerned with methods of studying physical, chemical, and physiological development and the receptor functions. This is followed by six chapters on the study of perception, learning, problem solving, thought, language, and communication. The next five chapters concern projective techniques, the measurement of children's attitudes and values, motivation and affect, and the appraisal of personality characteristics. The book concludes with chapters on the child's social behaviour and environment, interpersonal behaviour, the measurement of family-life variables, and the contributions of anthropology to the methods of study of child rearing.

This is definitely not a book for most paediatricians. It is a book for child psychologists in the research field. It is thoroughly scientific and authoritative, and for child psychologists it would seem likely to fill an important gap in the literature and be an invaluable book of reference.

R. S. ILLINGWORTH.

BONE TUMOURS

Neoplasms of Bone and Related Conditions. Etiology, Pathogenesis, Diagnosis, and Treatment. By Bradley L. Coley, M.D. Second edition. (Pp. 863+xv; illustrated. $30.) New York: Paul B. Hoeber, Inc.

The second edition of Dr. Coley's textbook is a revised and enlarged version of the first. The well-planned format has been retained. The author has revised the text and added to the illustrations, which are mainly radiographs; the references have been brought up to date; and the chapters on radiotherapy have now been written by a specialist in this field.

The book remains essentially a clinical treatise. The emphasis is placed on diagnosis and differential diagnosis from the surgeon's point of view, but there is, as well, extensive consideration given to treatment. A large part of the book is devoted to those conditions which are so often confused with primary tumours of bone. Stress is laid on the assistance given by radiological examination and on the necessity for confirmation of diagnosis by biopsy. The space devoted to the pathology of the lesions discussed, however, is frequently limited. In most instances the pathological concepts propounded are based on Jaffe, though other views are presented as well. In the case of the more unusual and rare bone diseases, pathological concepts and interpretations are sometimes not those generally accepted, and occasionally it is difficult to form an idea of Dr. Coley's own concept of a condition: myxoma is such an example. The acceptance of Jaffe's juxta-cortical chrondroma but the rejection of Lichtenstein and Hall's periosteal chondroma appears contradictory.

The book is written in a pleasing style. Not enough of the many references listed are quoted in the text, and sometimes it becomes difficult to separate Dr. Coley's experience from that of other people, with the result that the work is of a rather didactic nature, and the sense of participation in Dr. Coley's own extensive experience is regrettably obscured. This book has been one of the standard clinical reference works on bone tumours, and should continue to be so. It is a large work, carefully planned, and stands as a record of the abilities of Dr. Coley, and of the inspiration he received from his father before him.

PAUL D. BYERS.

BLOOD GROUPING

Advances in Blood Grouping. By Alexander S. Wiener, M.D., F.A.C.P. (Pp. 549+xii; illustrated. $11.) New York and London: Grune and Stratton. 1961.

A new book from Dr. Wiener's laboratory represents an important scientific event for all blood-group workers. Readers of this latest addition to his publications will find much valuable information within it. Like *Rh-Hr Blood Types*, published in 1954, it consists of a collection of reprints of previously published papers by the author and his co-workers, but this new volume covers a wider field. Though much space is given to the Rh system, other main blood-group systems are considered. The detection of gamma-globulin deficiency, the care of babies suffering from haemolytic disease of the newborn, and the management of acquired haemolytic anaemia are some of the clinical problems which are included. Medico-legal workers will appreciate the series of five papers dealing with the use of blood-groups in their specialty. Indeed, anyone whose work is in any way connected with blood groups would find in this book a great deal of useful information.

It is a great pity, however, that Dr. Wiener has not found time to write a new textbook rather than to issue a further collection of papers. Inevitably such a volume as the present one must contain a great deal of repetition. Each paper, having been published separately, naturally has a separate introduction, and since successive papers deal with closely related subjects the introductions are bound to have much in common. As most readers will already know, Dr. Wiener has strong objections to the CDE nomenclature of Rh blood groups, and it is only right that he should want to air his views on the subject. Nevertheless, it is a great pity that, through the very nature of this volume, paper after paper should deal, at least in part, with the very same problem. The reader, ploughing through the reiteration, may well miss much valuable information. Moreover, if it were possible to produce a new textbook, or a new and up-to-date edition of his earlier *Blood Groups and Transfusion*, last revised in 1943, the elimination of the verbosity would reduce the size, and therefore perhaps the price, of the book, thus enabling the individual British worker to purchase it. Until such a volume appears, however, we would recommend the present volume to every pathological and blood-grouping laboratory as a most useful work of reference.

K. L. G. GOLDSMITH.

STRUCTURE OF THE EYE

The Structure of the Eye. Proceedings of the Symposium held April 11–13, 1960, During the Seventh International Congress of Anatomists, New York. Edited by George K. Smelser. (Pp. 570+xv; illustrated. £5 7s. 6d.) New York and London: Academic Press, Inc.

The appearance of this book is an event of more than ordinary interest in ophthalmology, as it reflects, perhaps to a greater degree than any other recent publication, modern trends in eye research. Though it would be unjust to decry the contributions of the older workers—usually men who enthusiastically devoted such time as they were able to original work—it must be admitted that their writings often, and not unnaturally, bore the stamp of the untrained investigator. To-day this field has been invaded by experts in almost every scientific discipline, who, as full-time workers with all the advantages of modern scientific equipment, are able to concentrate on the particular and general problems that present in the eye. In this beautifully produced record of the proceedings of a symposium on the fine structure of the eye, held during the seventh international Congress of Anatomy in New York last year, the fruits of this development are abundantly clear.

There are 37 original communications, almost all of outstanding quality—as indeed was to be expected, since the participants are already well-known for their distinguished work. No fewer than 16 of these papers are by the new histologists—the electron-microscopists—who unlike their predecessors may not rest content with purely descriptive accounts, but are compelled by the fundamental nature of their observations in molecular architecture to speculate on its functional significance. These papers make exciting reading; especially as one realizes that we are as yet only on the fringe of the discoveries that these effective new techniques can provide, and that the changes wrought by disease still wait patiently to be revealed. Other papers report histochemical observations on the retina, the pecten oculi, and on the corneal endothelium; there are immunological studies on the lens; autoradiographic findings in

the corneal endothelium, and more conventional—but not less valuable—work on the morphology of the trabecular meshwork and retinal glia. The editor is to be congratulated on a fine production, and there can be no doubt that this book will be in great demand not only by those who seek knowledge but also by those who enjoy it.

NORMAN ASHTON

STUDENTS' MEDICAL HISTORY

A Prelude to Medical History. By Félix Martí-Ibáñez, M.D. (Pp. 253+xix. $5.75.) New York: MD Publications, Inc. 1961.

The pen, or in this case the tape recorder, of Dr. Martí-Ibáñez is indefatigable in disseminating his store of knowledge of medical history. His latest book is based on lectures given to medical students at the New York Medical College, Flower and Fifth Avenue Hospitals. His purpose was not to produce medical historians but to help and stimulate men and women to become better physicians; for he wisely emphasized that "the history of medicine is not merely history, it is above all *medicine*." So Osler, Sigerist, Sarton, Singer, and Fulton taught, but the lesson still needs to be driven home. The book is therefore appropriately entitled; it is an introduction to and not a history of medicine. In 253 pages full of erudition, wide reading, wit, and imagination the author gives a panorama of medical history, ranging from palaeomedicine to atomic and space medicine. In so rapid a review, inevitably, some statements will not secure general acceptance. For example, it is not the case that the only recognized specialists in England at the end of last century were paediatricians and dermatologists (p. 183). Sir Frederic Still was then the only whole-time paediatrician, and what of the neurologists and the heart and pulmonary specialists? Again, team research work has not altogether displaced the individual research worker, as witness the discovery of the therapeutic efficacy of the sulphonamides by Domagk and of penicillin by Fleming.

This is an excellent book to put into the hands of a medical student. The author gives at the end a list of books on the history of medicine which may encourage the reader to pursue his study of the subject further.

ARTHUR S. MACNALTY.

GARGOYLISM

Gargoylism. By J. F. van Pelt, M.D. (Pp. 153; illustrated.) Sittard, Holland: Alberts' Drukkerijen. 1960.

Dr. van Pelt has based his monograph on a study of 18 Dutch patients with gargoylism, all of them affected with the severe type. Six patients come from a single family, showing a typical sex-linked recessive pattern of inheritance. Necropsy reports are given for five of the patients. The clinical and pathological features of the disorder are carefully described and related to those in the literature, with special reference to the neuropsychiatric signs. Dr. van Pelt draws attention to two new points: the loss of vestibular function in patients who still have some hearing, and the presence of corneal opacity in one of his patients in the family showing sex-linked recessive inheritance. Hitherto the presence of corneal opacity has been regarded as one of the distinguishing features of the forms of gargoylism determined by an autosomal recessive gene

C. O. CARTER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

A Textbook of Pathology. An Introduction to Medicine. By William Boyd, M.D., Dipl.Psychiat., M.R.C.P.(Edin.), Hon. F.R.C.P.(Edin.), F.R.C.P.(Lond.), F.R.C.S.(Can.), F.R.S.(Can.), LL.D.(Sask.), (Queen's), D.Sc.(Man.), M.D.(Oslo). Seventh edition. (Pp. 1,370; illustrated. 126s.) London: Henry Kimpton. 1961.

Manson's Tropical Diseases. A Manual of the Diseases of Warm Climates. Edited by Sir Philip H. Manson-Bahr, C.M.G., D.S.O., M.A., M.D., D.T.M.&H.Cantab., F.R.C.P.Lond., M.D. (Malaya-Hon. Causa). Fifteenth edition. (Pp. 1,177+xiv; illustrated. 84s.) London: Cassell. 1960.

Introduction to Parasitology. With special reference to the parasites of man. By the late Asa C. Chandler, M.S., Ph.D., and Clark P. Read, M.A., Ph.D. Tenth edition. (Pp. 822+ix; illustrated. 78s.) New York and London: John Wiley and Sons, Inc. 1961.

A Chemical Approach to Food and Nutrition. By Brian A. Fox, B.Sc., A.R.I.C., and Allan G. Cameron, B.Sc., A.R.I.C. (Pp. 326. 30s.) London: University of London Press Ltd. 1961.

Medicine and the Navy 1200-1900. Volume III—1714-1815. By Christopher Lloyd, F.R.Hist.S., and Jack L. S. Coulter, F.R.C.S. (Pp. 402+xi; illustrated. 50s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

A Short History of Clinical Pathology. By W. D. Foster, M.D.Cantab. With a chapter on the organization of Clinical Pathology to the present day by S. C. Dyke, D.M., F.R.C.P. (Pp. 154+xii; illustrated. 27s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1961.

Some Aspects of Obliterative Vascular Disease of the Lower Limb. By J. A. Gillespie, M.D., Ch.M., F.R.C.S., and D. M. Douglas, Ch.M., F.R.C.S. (Pp. 136+vii; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1961.

The Encyclopaedia of Sexual Behaviour. Volumes I and II. Edited by Albert Ellis, Ph.D., and Albert Abarbanel, Ph.D. (Pp., Vol. I, 1-574+xxii; Vol. II, 575-1059+viii. £7 15s. the set.) London: William Heinemann. 1961.

Radiobiology. Proceedings of the Third Australian Conference on Radiobiology held at the University of Sydney, 15-18 August, 1960, by the Australian Radiation Society. Edited by P. L. T. Ilbery. (Pp. 314+xi; illustrated. 63s.) London: Butterworths. 1961.

Notes on Leprosy. By Dharmendra, M.B., B.S., D.B.(Lond.). (Pp. 203+vi; illustrated. No price.) New Delhi, India: The Ministry of Health, Government of India. 1960.

Atti della Accademia Medica Lombarda. Milan, 17 and 18 December 1960. Volume 15. ***Simposio su "la Terapia delle Ipertensioni Arteriose Primarie."*** Edited by W. Montrosi. (Pp. 553–906; illustrated. L. 5,000.) Milan: Stamperia Cesare Tamburini. 1961.

Dermatologie und Venerologie. Einschliesslich Berufskrankheiten Dermatologischer Kosmetik und Andrologie. Volume I, part I. Edited by Professor Dr. med. H. A. Gottron and Professor Dr. med. W. Schönfeld. (Pp. 743+xvi; illustrated. DM. 187.) Stuttgart: Georg Thieme Verlag. 1961.

Explorations into the Nature of the Living Cell. By Robert Chambers and Edward L. Chambers. A Commonwealth Fund Book. (Pp. 352+xxiv; illustrated. 64s.) Cambridge, Massachusetts: Harvard University Press. London: Oxford University Press. 1961.

Heredity in Ophthalmology. By Jules François. Translated from the French edition entitled *L'Hérédité en Ophtalmologie*, by Jules François. (Pp. 731; illustrated. 172s. 6d.) St. Louis, Missouri: The C. V. Mosby Company. London: Henry Kimpton. 1961.

Index zum Diabetes Mellitus. Eine Internationale Bibliographie. By Professor Dr. med. et phil. Joseph Schumacher. (Pp. 878+xlviii. DM. 286.) Munich and Berlin: Verlag von Urban and Schwarzenberg. 1961.

Entretiens de Physio-Pathologie Respiratoire. Fourth session, 2, 3, 4, and 5 October, 1960, held at Nancy. (Pp. 724–1164; illustrated. No price.) Nancy, France: Faculté de Médicine. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY AUGUST 19 1961

EARLY MATURING AND LARGER CHILDREN

The ever earlier maturation of children is one of the most astonishing occurrences in human biology to-day. The particularly surprising features of it are its magnitude and its regularity. C. Roberts, a general practitioner and industrial medical officer of Uxbridge, who was the first person to make a substantial study of children's growth in this country, wrote in 1876 that "a factory child of the present day at the age of 9 years weighs as much as one of 10 did in 1833 . . . each age has gained one year in 40 years."[1] This trend has continued up to the present, so that a child aged 9 in 1960 weighs about the same as a child of 11 in 1900. The trend has occurred in all Western European countries for which we have information (Norway, Sweden, Germany, Austria, France, Switzerland, Italy), in the United States, Canada, New Zealand, and Australia, and to only a slightly lesser extent in Japan, at least since 1900. Most of the data on children's heights and weights come from schools, so that the documentation is worse at ages under 6 than at ages 6 to 15. But it seems that much of the gain in height and weight is already present by age 6 in the European children. In Japanese children, however, the gain is concentrated in the years 6 to 14,[1] and in British children, according to the latest London County Council report,[2] the gain from 1954 to 1959 seems to be exclusively at ages 8 to 14, no change having occurred at ages 5, 6, and 7.

Two factors contribute to this increase in children's size. Children mature earlier, and boys on average practically complete their growth in height by 17 nowadays as against 23 or more in 1900. Moreover, the final adult height reached has itself become greater, though not to the same extent as the height, say, of children aged 11. The earlier maturing can best be seen in the statistics for age of menarche or first menstrual period. J. M. Tanner has marshalled the data stretching back to 1840.[1] In Norway and Sweden at that time the average girl reached menarche at age 17 or later; nowadays the figure is about 13½. Similar trends are visible in data from Germany, Finland, and the United States. Reliable British statistics on this matter began only recently, but they follow the general trend with some precision and without any sign that it is slowing up. The last two London County Council surveys, conducted at an interval of five years, give an average difference of almost exactly two months. Thus, the reduction in age at menarche has been continuous at about four months per decade, or roughly one year per generation.

The general increase in adult height is now equally well established, though a contrary view was sometimes taken in the past owing to the examination then of insufficient data. It is essential to measure the full adult height and not height at, say, 20; nowadays this would suffice, but formerly it was still short of the maximum. Fortunately we have data which tell us the extent of the gain from 20 to 26 at various times, most notably in the extraordinary Norwegian soldiers' records which go back continuously to 1741 and include serial data on men followed up from 17 to 25 years of age.[3] Adjustments by means of these and subsequent data make it clear that in Western Europe adult height has been increasing by approximately 1 cm. per decade or roughly an inch a generation since 1850. Before 1850 the increase seems to have been somewhat less.

The reasons for the trend are not entirely clear. The earlier maturing is usually put down to better nutrition, and probably with reason. All the same, the increase has by no means been confined to the less favoured social classes; indeed, these have gained only a little more than the more favoured ones. Schoolboys at Marlborough College, for example, mostly drawn from the homes of professional or managerial people, were reported by Sir Francis Galton as being on average 166.2 cm. (5 ft. 4 in.) at 16.5 years in 1873.[1] Seventy years later the average at the same age was 177.0 cm. (5 ft. 10 in.),[4] an increase of 1.5 cm. per decade, which is about two-thirds the general rate of increase over the whole population at that age.

Better nutrition, or the effects of less disease, have also been given as causes for the increase in final adult height. Probably they are responsible for at least part of it. An alternative or supplementary explanation was suggested some years ago by G. Dahlberg, to the effect that the increase in height was the result of heterosis, or hybrid vigour. What Dahlberg's proposition amounts to is that persons whose genes for stature are equally mixed—tall,

[1] Tanner, J. M., *Growth at Adolescence*. 2nd ed. Oxford. 1961.
[2] Scott, J. A., *Report on the Heights and Weights of School Pupils in the County of London in 1959*. London County Council. 1961.
[3] Kiil, V., *Skr. norske Vidensk-Akad., I. Mat.-nat. Kl.*, No. 6, 1939, 175 pp.
[4] Boyne, A. W., in *Human Growth*, ed. J. M. Tanner. Oxford. 1960. (*Symp. Soc. Study Hum. Biol.*, 3, 97.)
[5] Hulse, F. S., *Arch. suisses Anthrop. gén.*, 1957, 22, 103.

short, and intermediate—will be nearer in height to those whose genes are mainly for tall stature, instead of being exactly half-way between tall and short. At the time there was little evidence for this in man, and indeed the evidence is still equivocal, but at least suggestive.[5] If we accept this evidence, then increased outbreeding—that is, an increased tendency for persons to marry people outside their own village rather than within it—could have caused the increase in height. There are indeed data to show that the degree of outbreeding has been steadily increasing in Europe ever since the introduction of the bicycle. Whatever the true explanation, the trends towards earlier maturing and increase in adult height seem still to be continuing, and their causes deserve close study.

NARCOLEPSY

Although narcolepsy is uncommon, its correct diagnosis is important because it is embarrassing and at times even dangerous to the sufferer and the response to treatment is usually good. Recently G. Bowling and N. G. Richards[1] recorded 75 cases seen in nine years at the Cleveland Clinic. Men were affected rather more frequently than women, and the disorder started by the third decade in 54 patients. In its fully developed form there are four components of the syndrome : attacks of narcolepsy, cataplexy, sleep paralysis, and hypnagogic hallucinations ; but these two latter are only occasionally present. The attacks of narcolepsy, which occurred in all the patients, are episodes of excessive and often irresistible sleepiness lasting from a few minutes up to several hours, but the patients can usually be awakened without difficulty. These sleep attacks occur most commonly at times when normal people might go to sleep—after a heavy meal, in a dull lecture, or when doing monotonous work—but they also occur at inappropriate times, such as in the middle of a meal, during physical activity, or while driving a car, and several of the authors' patients had serious accidents in this way. Cataplexy occurred in 50 of the 75 patients and usually started at about the same time as the narcoleptic attacks, though in one patient the episodes of excessive sleepiness had been occurring for 16 years before the first attack of cataplexy. The cataplectic attack is precipitated by an emotional stimulus, most commonly laughter, but sometimes anger or surprise, and consists in a sudden weakness and loss of tone in the muscles. This varies in degree from a subjective feeling of weakness to an actual weakness so great that the sufferer falls helpless to the ground, but without any impairment of consciousness. In such an attack the pupils may lose their reaction to light, the tendon reflexes may be diminished or abolished, and the plantar responses may become extensor.[2] The whole episode is usually over in less than a minute. Here, as with narcolepsy, there is an exaggeration of a normal response—as the phrase " helpless with laughter " indicates.

Sleep paralysis was only recorded in ten of the Cleveland series. This is a transient loss of muscle power as the patient is going off to sleep or when he wakes up, and usually lasting a minute or so, but in one patient the weakness lasted for an hour ; frequently someone touching the patient lightly will immediately restore him to normal. This condition in mild degree is not uncommon in normal people who do not suffer from narcolepsy or cataplexy and would seem to be closely related to " night-nurses' paralysis." Hypnagogic hallucinations occurred in four patients. They are vivid visual or auditory hallucinations occurring just as the patient is going off to sleep and may coincide with sleep paralysis.

The diagnosis of narcolepsy depends entirely on taking an accurate history, as there are no abnormal physical findings and special investigations are of no help. The electroencephalogram is usually normal except for a sleep record during the actual attacks of narcolepsy. Bowling and Richards found excessive slow activity in some of their patients, but in others the record was normal. The main point in diagnosing narcolepsy is to distinguish the compelling urge to sleep occurring in attacks, which is characteristic of the disease, from the persistent feeling of fatigue and apathy which may occur in neurosis and in some organic conditions, and from the persistent hypersomnia which may occur with lesions of the mid-brain and hypothalamus, with raised intracranial pressure, and with some disturbances of metabolism. When a history of cataplexy can be obtained, the diagnosis is made easier, though only direct questioning may elicit it, as some patients are reluctant to mention a symptom which seems to them somewhat ridiculous.

The Cleveland workers found no clinical evidence of progressive neurological disease in their 75 patients. This is certainly true of the majority of cases of the narcolepsy–cataplexy syndrome, but this syndrome has been known to follow encephalitis lethargica, so it is advisable to inquire closely for other evidence of hypothalamic disturbances and, if any are found, to investigate the patient further. Idiopathic narcolepsy usually responds fairly well to treatment with amphetamine and dexamphetamine (sometimes best given in delayed-release tablets) and ephedrine. The adequate dose may be a large one, and some trial is usually needed before the best dosage is found.

[1] Bowling, G., and Richards, N. G., *Cleveland Clin. Quart.*, 1961, **28**, 38.
[2] Brain, W. R., *Brit. med. J.*, 1939, **2**, 51.

BENIGN HODGKIN'S DISEASE

The clinical course of Hodgkin's disease is very variable: some patients progress to generalized disease a few months after the first group of glands have enlarged, others remain in good health for many years, with a localized glandular swelling as their only symptom. H. Jackson[1] reported in 1937 a group of cases in which the disorder that he called "early Hodgkin's disease" often remained entirely unaltered for twenty or more years. He was able to distinguish this variant from common Hodgkin's disease on the histological appearance of the lymph-node biopsy. Later, Jackson and F. Parker[2] used the term "Hodgkin's paragranuloma" for this condition, and A. H. T. Robb-Smith[3] described an apparently similar lesion as "lympho-reticular medullary reticulosis." C. V. Harrison[4] called it "benign Hodgkin's disease," G. Lumb[5] "reticular lymphoma," A. M. Jelliffe and A. D. Thomson[6] "Hodgkin's disease grade I," and W. St. C. Symmers[7] "indolent Hodgkin's disease." But, despite the many different names, the histological descriptions given by these pathologists to their own lymph-node biopsies were all very similar.

P. J. Dawson and C. V. Harrison[8] have now collected a series of 44 cases, all of which have been followed for four years, and many for much longer. In most of them the disease began between the ages of 15 and 35 years and there were more than twice as many men as women. The glands of the neck were involved in most of the cases. The glands were discrete and firm, and under the microscope were seen to have lost most of their architectural pattern, though in many of them a small area of normal tissue remained. Neither the necrosis nor the fibrosis of classical Hodgkin's disease was found, but there was often a delicate meshwork of reticulin fibrils. Sternberg–Reed mirror-image giant cells and reticulum cells were always present, but at least 80% of the cells were small lymphocytes. Eosinophils, neutrophil polymorphs, or plasma cells were seen only in a few biopsies and then only in small numbers. By way of comparison, Dawson and Harrison examined lymph-node biopsies from 43 cases of classical Hodgkin's disease. In these the proportion of reticulum cells to lymphocytes was always more than 35%, whereas in benign Hodgkin's disease it did not exceed 20%.

Benign Hodgkin's disease usually follows a slow course. Jackson and Parker have followed one case for 38 years from the onset of the disease and Dawson and Harrison another for 26 years. They have calculated the 5-year survival rate at 93% and the 10-year rate at 85%. Left untreated, many cases show, after a varying number of years, a transition to classical or sarcomatous Hodgkin's disease. This suggests that benign Hodgkin's disease is merely an uncommon variant of the classical condition and has probably the same aetiology. Whether the epithet "benign" should be applied to a disease which may progress to sarcoma is doubtful. Nevertheless, with energetic radiotherapy it appears to be possible to effect a permanent cure in many of those in whom the diagnosis is made.

THE CONTINUING PROBLEM OF GONORRHOEA

The number of patients with gonorrhoea attending venereal-disease clinics has been steadily increasing by about 12% each year since 1956. The figures for 1959 equal those for 1939, and it is clear that the disease is not being controlled.[1] This failure is not peculiar to Great Britain, and a recent review by T. Guthe[2] emphasizes the seriousness of the situation as a world problem.

Three prerequisites for combating any infectious disease are: rapid and exact means of diagnosis, identification of infectious carriers, and an effective means of treatment. The symptoms of gonorrhoea in the male are usually sufficiently acute to make patients seek medical care; in women, the disease is often latent and repeated attempts to culture the gonococcus may be necessary before the diagnosis can be made. It is accepted that cultural methods are superior to the examination of stained smears as a means of diagnosis, particularly in women.[3] The gonococcus is not a very easy organism to grow, and it is readily overgrown by the many other organisms found in the genital tract. E. M. L. Crookes and R. D. Stuart[3] have recommended the incorporation of 10 units/ml. of aerosporin in culture media; this was found to inhibit overgrowth by coliforms but not by proteus or other organisms. Atypical strains of gonococci which grow very poorly and show little or no fermentation of glucose on primary isolation are sometimes found. A. Reyn and M. W. Bentzon,[4] who noted an unusually high incidence of these strains in Denmark in 1957–8, have suggested that they may be

[1] Jackson, H., *Surg. Gynec. Obstet.*, 1937, **64**, 465.
[2] —— and Parker, F., *New Engl. J. Med.*, 1944, **230**, 1; **231**, 35 and 639.
[3] Robb-Smith, A. H. T., in S. C. Dyke (Ed.) *Recent Advances in Clinical Pathology*, 1947, p. 360, London.
[4] Harrison, C. V., *J. Path. Bact.*, 1952, **64**, 513.
[5] Lumb, G., *Tumours of Lymphoid Tissue*, 1954, p. 58, Edinburgh.
[6] Jelliffe, A. M., and Thomson, A. D., *Brit. J. Cancer*, 1955, **9**, 21.
[7] Symmers, W. St. C., in R. W. Raven (Ed.) *Cancer*, 1958, Vol. 2, p. 478, London.
[8] Dawson, P. J., and Harrison, C. V., *J. clin. Path.*, 1961, **14**, 219.

[1] *Brit. med. J.*, 1961, **2**, 224.
[2] Guthe, T., *Bull. Wld Hlth Org.*, 1961, **24**, 297.
[3] Crookes, E. M. L., and Stuart, R. D., *J. Path. Bact.*, 1959, **78**, 283.
[4] Reyn, A., and Bentzon, M. W., *Bull. Wld Hlth Org.*, 1961, **24**, 333.
[5] Deacon, W. E., Peacock, W. L., Jr., Freeman, E. M., and Harris, A., *Proc. Soc. Exp. Biol. (N.Y.)*, 1959, **101**, 322.
[6] —— —— —— and Bunch, W. L., *Publ. Hlth Rep. (Wash.)*, 1960, **75**, 125.
[7] Keighley, E., *Lancet*, 1960, **2**, 253.
[8] Garson, W., and Barton, G. D., *Publ. Hlth Rep. (Wash.)*, 1960, **75**, 119.
[9] Tauber, H., and Garson, W., *Proc. Soc. exp. Biol. (N.Y.)*, 1957, **95**, 669.
[10] —— *J. biol. Chem.*, 1959, **234**, 1391.
[11] *Report of M.R.C. Working Party on the Resistance of Gonococci to Penicillin, 1961. Lancet*, 1961, **2**, 226.
[12] Curtis, F. R., and Wilkinson, A. E., 1961. Unpublished data.
[13] Roiron, V., Rasetti-Nicod, G., and Durel, P., *Ann. Inst. Pasteur*, 1961, **100**, 445.

connected with antibiotic therapy. These strains grew poorly on enriched media on which lyophilized strains which had been isolated in 1944 before the gonococcus had been exposed to penicillin grew normally.

Under the most favourable conditions isolation and identification of the gonococcus takes several days to accomplish, and if the fluorescent antibody techniques introduced by W. E. Deacon and others[5,6] serve to speed the process they may prove valuable. Though the results do not show any marked superiority over conventional cultural methods in terms of the number of positive findings, they are important because they give a quick answer. Further information about the specificity of the method is needed, as it is known that other *Neisseria* organisms besides the gonococcus are sometimes found in the genital tract.

Identification of infectious carriers may present difficulties, for the promiscuous female with latent gonorrhoea is often an important reservoir of infection, and these people are sometimes uncooperative and frustrate attempts to bring the disease under control. In an examination of 1,921 women admitted to Holloway Prison, E. Keighley[7] found that 11% were suffering from gonorrhoea. A third of the 464 prostitutes sent to the prison in 1958 had gonorrhoea, and in those in the teenage groups the incidence was 48.9%.

When patients are brought under medical care, how effective are our present methods of investigation? W. Garson and G. D. Barton[8] state that studies by the United States Public Health Service indicated that clinical information plus the bacteriological examination of smears and cultures resulted at best in the diagnosis of 50–75% of those females having gonorrhoea. As they phrase it, "the most sensitive, practical indicator of gonorrhoea in the female is the anterior urethra of a susceptible male."

For the other major venereal infection, syphilis, the use of routine serological testing is a well-established method of detecting unsuspected cases. The complement-fixation test for gonorrhoea finds little favour at present, but recent work on the immunochemistry of the gonococcus has revived interest in the problem. H. Tauber and W. Garson[9] isolated a nucleoprotein from the gonococcus which has the properties of an endotoxin, and have since shown[10] that the bulk of the toxicity is associated with a lipopolysaccharide. If a specific serological test could be developed which indicates active gonococcal infection, it would provide a most useful means of investigation.

The gonococcus has shown unexpected resourcefulness in developing tolerance to penicillin. In Great Britain relatively insensitive strains associated with failure to respond to treatment with penicillin were first noted in London in 1957. Subsequent surveys in other areas have shown that such strains are widely distributed throughout the country, though the highest level of resistance reached in 1957 has not yet been exceeded.[11] Streptomycin has been the drug of second choice for the treatment of gonorrhoea, but it appears that resistance to this antibiotic is also increasing. F. R. Curtis and A. E. Wilkinson[12] have found that in 1957 only 1.2% of strains were resistant to streptomycin *in vitro*; in 1960–1 the figure had risen to 7.2%. Streptomycin has been widely used in France for the treatment of gonorrhoea since 1951, and V. Roiron and colleagues[13] have recently reported that 28% of strains are now resistant. Gonococci resistant to streptomycin show, in contrast to their behaviour with penicillin, complete resistance to the antibiotic. Both Reyn and Bentzon and Curtis and Wilkinson have noted that there is a correlation between resistance to penicillin and resistance to streptomycin. Many of the strains only inhibited by 0.125–0.5 unit/ml. penicillin were completely resistant to streptomycin, whereas resistance to the latter drug is uncommon among strains which are sensitive to penicillin. Fortunately the gonococcus is still sensitive to the tetracyclines, and it has apparently largely recovered its sensitivity to the sulphonamides. It still presents many challenging problems which must be answered before we can hope to control the disease it causes.

CARCINOMA AND CUSHING'S SYNDROME

The occurrence in patients showing signs of increased adrenocortical activity of malignant tumours in organs unrelated to the pituitary–adrenal axis has been described often enough to suggest that the association is more than coincidental.[1] Forty-three such cases have already been reported; nevertheless, the association must be rare, for there was no mention of it in the papers describing two large series of cases of Cushing's syndrome.[2,3] The patients who developed carcinoma in association with adrenocortical hyperactivity have usually shown signs of Cushing's syndrome.[1,4] Other patients have had only hypokalaemic alkalosis, but had they survived longer they might have progressed to Cushing's syndrome.[5] Whereas severe hypokalaemic alkalosis is unusual in uncomplicated Cushing's syndrome[2,3,6,7] it was an important feature in 19 out of 23 cases of the syndrome associated with malignant tumours of other organs.[1] Electrolyte disturbances of this degree might suggest that the secretion of aldosterone is increased, but this was not so in four out of five cases in which the hormone was measured.[4] Severe hypokalaemia without aldosteronuria has been noted also in Cushing's syndrome due to adrenal carcinoma.[8,9] Available data do not suggest any essential difference in steroid metabolism between these cases and those of

1 Allott, E. N., and Skelton, M. O., *Lancet*, 1960, **2**, 278.
2 Plotz, C. M., Knowlton, A. I., and Ragan, C., *Amer. J. Med.*, 1952, **13**, 597.
3 Soffer, L. J., Iannacconne, A., and Gabrilove, J. L., ibid., 1961, **30**, 129.
4 Bagshawe, K. D., *Lancet*, 1960, **2**, 284.
5 —— ibid., 1960, **2**, 287.
6 Bayliss, R. I. S., *Proc. roy. Soc. Med.*, 1957, **50**, 761.
7 Mason, A. S., Richardson, J. E., and King, C. E., *Lancet*, 1958, **2**, 649.
8 Garrod, O., Tait, J. F., and Chalmers, T. M., *Proc. roy. Soc. Med.*, 1957, **50**, 770.
9 Muller, A. F., *Aldosterone*, 1958, edited by A. F. Muller and C. M. O'Connor, London, p. 27.
10 Kovach, R. D., and Kyle, L. H., *Amer. J. Med.*, 1958, **24**, 981.
11 Warren, F. L., *Cancer Res.*, 1945, **5**, 49.
12 Webster, G. D., Touchstone, J. C., and Suzuki, M., *J. clin. Endocr.*, 1959, **19**, 967.
13 Hökfelt, B., Sjogren, B., and Falkheden, T., *Acta endocr. (Kbh.)*, 1959, **31**, 175.
14 Di Ferrante, N., Magilocca, R., Natoli, A., and Zilli, E., *Policlinico, Sez. Prat.*, 1951, **58**, 1349.
15 Kaplan, L. I., Sokoloff, L., Murray, F., and Stevenson, L. D., *Arch. Neurol. Psychiat.*, 1949, **62**, 696.
16 Parrish, J. A., *Lancet*, 1960, **2**, 603.

uncomplicated Cushing's syndrome due to adrenocortical hyperplasia. Whatever may be the factor in carcinoma which potentiates hypokalaemia, it is not related to the size of the tumour or the presence of secondary deposits in the liver, which were an inconstant finding in these cases.[4] In order of frequency the tumours associated with Cushing's syndrome have been carcinoma of bronchus (21 cases), thymus (10 cases), and pancreas (6 cases).[1] The bronchogenic carcinomas have been anaplastic or of oat-cell type.[1] Isolated reports have appeared of Cushing's syndrome associated with carcinoma of colon,[11] prostate[12] and thyroid,[13] seminoma of the testis,[14] and sympathicoblastoma.[15,16] Most of the affected patients have been younger, and the proportion of women higher, than the average for the type of cancer.[1] Though secondary deposits may be found in the adrenal glands they are not an essential feature of the association. In any event, adrenal metastases are so common in patients without adrenal dysfunction that their occurrence is unlikely to be relevant in this connexion.

In this issue of the *Journal* (p. 490), Drs. J. R. Billinghurst, A. K. Thould, O. P. Galpin, and J. M. Hinton report two more cases of Cushing's syndrome associated with bronchogenic carcinoma. One patient presented with psychosis and thrombocytopenic purpura which proved to be due to metastases in bone-marrow, the other with asymmetrical neuromyopathy. The authors discuss briefly some theories which have been put forward to explain the association, but these are speculative at present and unsupported by experimental data.

In man, there is no evidence to suggest that exposure to excessive glucocorticoid secretion or therapy can precipitate malignant disease. The deviations in age and sex from the average for the type of carcinoma which may occur in association with Cushing's syndrome favour a causal relationship between the two disorders. But each may precede the other in onset, at least clinically, and it is hard to say which is primary. If carcinoma is the primary factor, why do tumours of such diverse organs as the bronchus, thymus, and pancreas have this common effect? As yet, we are far from understanding the significance of this association. Meanwhile clinicians should be alert to the possible presence of extra-adrenal carcinoma in middle-aged patients presenting with Cushing's syndrome.

MISHAP AT A RESERVOIR

Urban householders seldom give much thought to the water supplied to their homes: they confidently rely on its continuing flow, its purity, and its freedom from pathogenic organisms. But behind the scenes there are occasional alarms and excursions which can give medical officers of health an anxious few days. Earlier this year Dr. M. B. McCann, medical officer of health of Worksop—a town with a population of nearly 35,000—had to meet an unusual emergency.[1] On March 11 the water engineer found that the level of the water in the town's 80-year-old, partially underground reservoir was falling rapidly, though the flow from the source (four deep boreholes) was normal. Investigation showed that a section of the concrete floor of the reservoir had fallen in and that Worksop's water was fast disappearing into the bowels of the earth. The crisis had to be met immediately.

The collapse of the floor of the reservoir was due to the poor quality of the concrete and its thinness, and attempts to close the hole temporarily proved unavailing. The next step was to pump the water direct from the source into the mains without the use of the reservoir, and large containers mounted on lorries were sent to the higher parts of the town where the pressure in the mains was insufficient. Meanwhile the public was warned by the police to use water with great economy, and within a few hours hundreds of householders telephoned for advice on such matters as whether they should withdraw the fires from their heating stoves. As a safety measure it was decided to increase the chlorination to 2 p.p.m. of chlorine, but while water was being pumped straight into the mains it proved difficult to maintain a uniform strength of chlorination, quite apart from the fact that the chlorinators often went out of action because of the varying rates of flow.

Unusually high coliform counts from some samples of water caused anxiety, and daily readings of chlorine in samples taken direct from householders' taps gave bewildering results—at one time reading 1.5 p.p.m. and at others nil. This, it transpired, was due to the failure of two small chlorinating stations to cope with the abnormal pressures resulting from the additional flow of water into the mains from a colliery, which was able to double its customary small contribution to the town's supply.

While the reservoir was being repaired the medical officer of health and his staff had the lessons of the Croydon typhoid epidemic in 1935 very much in mind, and blood, faecal, and urinary specimens (all negative) were taken from the thirty workmen employed. The workmen were also told they must come to the surface to use the lavatories. By April 22 the reservoir was in working order again, and the only untoward event during the crisis was the death of goldfish in various parts of the town owing to the occasional excess of chlorine in their water. Dr. McCann concludes his account of this public-health emergency by quoting the words of Sir John Charles: "There is an overall medical responsibility for the health aspects of water collection, treatment, and distribution, a responsibility which does not begin 'at the tap,' but extends from the actual source, whether above or below ground, to the consumer."

EPILEPSY AND DRIVING LICENCES

For years patients and doctors have been worried about the variability of practice in the issuing of driving licences to handicapped people, and especially epileptics, who are the only medical category specifically mentioned in the application form. Several years ago the

[1] McCann, M. B., *Monthly Bull. Minist. Hlth Lab. Serv.*, 1961, **20**, 122.

British Epilepsy Association asked medical officers of health about their current practices. They found a diversity of opinion and practice from one licensing area to another and general dissatisfaction with the present situation. Recently the Ministry of Transport has sent a memorandum to the Registration and Licensing Authorities, from which the following is quoted:

"The Department has received advice that epilepsy should be regarded as a continuing liability to recurrent epileptic attacks. It follows that a person who has, in the past, had one or more attacks of convulsions, or of disturbance of consciousness, in circumstances which are unlikely to recur need not necessarily be regarded as suffering from epilepsy. Certain people who may think that they have, or may have been regarded as having, suffered from epilepsy may, therefore, in fact not be suffering from epilepsy. In order to determine whether this is so, it is appropriate to take into account such matters as the frequency of attacks in the past and the duration of freedom from attacks since any treatment ceased.

"In any case of doubt as to whether an applicant for a driving licence, or the holder of a licence is debarred from holding a licence by reason that he is suffering from epilepsy, the Licensing Authority will, no doubt, consult the local County Council or County Borough Medical Officer of Health with a view to obtaining any specialist medical advice which may seem necessary in all the circumstances."

It would appear to follow from this note that patients who have had epilepsy in the past could be encouraged to apply, especially if they can obtain support from a recognized specialist. It is to be hoped that this will lead to some uniformity of practice, though no rule is laid down about the number of years of freedom from fits required before epileptics can be licensed. D. A. Pond and B. H. Bidwell's[1] survey on epilepsy in general practice in England included a question about car driving, and they estimated that there are about 6,500 drivers with epilepsy on the road. J. C. Phemister[2] had heard of only minor accidents among epileptic drivers. In contrast R. Hierons[3] was able to collect quite a number of cases, some of them more serious. But it is clearly impossible to estimate the number of accidents due to fits, for the facts are apt to be concealed.

The practice of issuing three-year licences means that drivers already licensed may continue to drive for some time after fits start for the first time or begin again after many years. The problem of disabling illness supervening during the period of being licensed is, of course, a general one. It is possible, for example, that heart disease and cerebral vascular disease leading to sudden inability to drive may be numerically more important causes of accidents than epilepsy. Patients with epilepsy are naturally reluctant to admit to suffering from what they often regard as a shameful disorder on a form which is scrutinized in the local council offices. But if they intend to drive a car then they must be prepared to face inquiries. The question on the form reads: "Do you suffer from epilepsy, or from sudden attacks of disabling giddiness or fainting? Read Note (F) and answer YES or NO." Note (F) says, "If you are in doubt as to your answer . . . you should get professional advice." It seems possible that more sufferers from epilepsy should get professional advice than in fact do so, and also possible that the advice might not be so unpalatable as some of them fear it would be.

[1] Pond, D. A., and Bidwell, B. H., *Epilepsia*, 1960, **1**, 285.
[2] Phemister, J. C., *Lancet*, 1961, **1**, 1276.
[3] Hierons, R., *Brit. med. J.*, 1956, **1**, 206.

BAROTRAUMA OF EXTERNAL AUDITORY CANAL

Since the war the glamour and fascination of underwater swimming and exploration have attracted an enthusiastic band of amateur frogmen. Like all sports, subaquatics carries with it special dangers and risks. Doctors who may be called upon to examine and treat these underwater adventurers must be familiar with all the physical and physiological implications of exposing the body to increased ambient pressures, so that an explanation of the mechanism by which one of the ill-effects of diving comes about is timely.

When people are exposed to a changing ambient pressure, as when diving or flying, it is necessary to ensure that the pressure of air in the middle ear remains in equilibrium with the pressure of air in the external auditory canal. If the eustachian tube should block when the ambient pressure is falling (a most unlikely occurrence), the drum would be expected to bulge outwards and eventually to burst when the pressure difference became great enough. Such a mechanism has been assumed to account for the ear injury known to divers as "reversed ear" or more correctly "reversed ear-drum," since the drum is normally concave on its outer surface.

In the *Journal* this week Surgeon Lieutenant A. Jarrett reports (page 483) that outward bursting of the drum in divers is a rare if not unknown occurrence and that the condition thought to be "reversed ear" in naval frogmen can occur after dives to less than 15 ft. (4½ m.), when the pressure difference even with a blocked eustachian tube across the two sides of a normal ear-drum would in any case be less than that required to burst it. Examination has revealed that, far from an outward bursting of the drum in these cases, there is not even an outward bulging to be seen. What may be seen in the external auditory canal is blood, subcutaneous petechiae, and blood-filled subcutaneous blisters or their remains if they have burst. Jarrett calls this condition the "reversed-ear syndrome"; a better term might be "barotrauma of the external auditory canal." He neatly shows that the syndrome directly results from the faulty design of the rubber suit and hood worn by naval frogmen. For instance, during a dive to 40 ft. a negative pressure of about 150 mm. Hg develops in the suit and hood; this is directly communicated to the external auditory canal, resulting in a passive dilatation of the blood vessels in the skin of this region and eventually in the formation of haemorrhagic bullae.

Divers could avert this syndrome by using properly designed frogmen suits. Amateurs should make sure that they use suits made of porous rubber, which prevents the development of negative pressure within the suit.

SCOPE AND FUNCTIONS OF AN AIRLINE MEDICAL SERVICE, WITH PARTICULAR REFERENCE TO B.O.A.C.

BY

K. G. BERGIN, O.St.J., M.A., M.D., D.P.H., F.R.Ae.S.
Director, Personnel and Medical Services, British Overseas Airways Corporation

Organization

B.O.A.C. employs approximately 20,000 personnel, of whom some 15,600 are based in the U.K. and 4,500 overseas. Approximately 2,800 of these are flying staff.

The main executive divisions of British Overseas Airways Corporation are the Flight Operations Department, responsible for flying the Corporation's aircraft; the Engineering and Maintenance Department, responsible at home and overseas for keeping the aircraft serviceable; and the Commercial Group, responsible for selling seats, handling passengers and cargo, and management of overseas stations. There are also branches dealing with finance, security, personnel, legal matters, staff welfare, press and public relations, motor transport, premises, and catering (ground and air) in addition to the medical branch. Several of these groups present special medical problems, as, for example, at certain large key stations overseas, such as New York, where there are particular community problems. In order to deal with the medical requirements of the diversity of personnel described above, medical officers are employed who are specially qualified by training and experience to care for those for whom they are responsible.

Because medical and personnel departments cover a lot of common ground, and it is obviously desirable that an individual employee should be treated as a human being with hopes, aspirations, fears, and potentialities, in 1959 it was decided that the Personnel and Medical Departments in B.O.A.C. should come under the unified control of the existing chief medical officer with the title of Director, Personnel and Medical Services, directly responsible to the Managing Director. The day-to-day running of the Medical Branch, however, is the responsibility of the senior medical officer (ground), and all personnel employed in the Branch, with a few exceptions, are ultimately responsible to him. A brief description of the various subdivisions of the Medical Branch is given in the following paragraphs.

Functional Responsibilities

Air Services Administration.—The senior medical officer (air) is in charge of medical services associated with the flying side of the organization, including medical care of flying staff, indoctrination in aviation medicine, supervision of conditions down the routes, and safety measures on all Corporation aircraft. He is also responsible for the conditions of carriage of invalid passengers and for training in first-aid of all flying staff, including stewards and stewardesses. He is assisted by two flying staff medical officers, both of whom have had extensive experience in the R.A.F. There is also a full-time research medical officer who is a qualified jet pilot, and whose duties are described later.

Ground Services Administration.—The senior medical officer (ground) is responsible for the day-to-day administration of the Branch as a whole and has particular charge of care of ground staff everywhere, families of overseas staff, problems of tropical medicine, industrial and preventive medicine, and the Corporation's immunization programme. He is assisted by a team of medical officers with specific duties related to these functions, including two industrial medical officers, an overseas staff medical officer, and an immunization medical officer, whose duties are referred to elsewhere. In addition, there is a general duties medical officer who relieves when medical officers are overseas on duty or on leave, etc.

Standards of Fitness.—It is essential that in the case of all grades of flying staffs and in many grades of ground staff the individual employee matches up to a certain standard of physical and psychological fitness according to the type of work required. These standards are formulated by the senior medical officer (ground) and the senior medical officer (air), respectively, and it is their duty to ensure that they are being applied by the medical officers responsible. To ensure that staff employed in those grades where definite standards of physical fitness are essential do in fact reach those standards, initial pre-employment medical examinations are followed—at varying intervals, according to the type of work—by routine medical examinations. These include a dental check, chest *x*-ray examination, audiometry, and laboratory tests, in addition to ordinary physical examinations. There are many instances where an individual not only falls far short of special requirements, but he or she may even fall short of what may be termed average good health. It is important that the physically handicapped should, if at all possible, be enabled to provide for himself, and all large organizations are compelled by law to employ a certain percentage of handicapped persons and encouraged to do rather better than that. Advice on the placement of these individuals is the responsibility of the industrial medical officer.

Flying Staff

Flying staff, of whom there are some 2,800, consist of pilots (including captains), navigating officers, engineer officers, radio officers, stewards, and stewardesses. Understandably the health, physical and psychological, of all the operating crew, particularly the pilot, is of the utmost importance, especially where safety in flying is concerned, and two whole-time medical officers with wide experience of the care of air crew both in the R.A.F. and in civil flying are employed to look after flying personnel. The first medical examination which a member of flying staff undergoes is his pre-employment one, and the standards are understandably very strict, in view of the exacting nature of the duties involved. It includes *x*-ray and pathological examinations. It is quite different from and unrelated to the examination a pilot has to undergo for his pilot's licence, which is the responsibility of the Ministry of Aviation. The Ministry examination is carried out to certain arbitrary international physical standards which are solely concerned with an individual's fitness to meet the requirements of a pilot's licence during the period of its validity—namely, six months—while the Corporation's examination is set to standards laid down by the employer and is, in addition, concerned with long-term employment on a world-wide basis.

Air-crew training is a very long process, and flying staff are in charge of expensive and highly technical equipment. It is therefore very important to the employer that a man is not merely fit to exercise the

privilege of his licence at a particular time, but is likely to remain so for the remainder of his active life with the Corporation. Secondly, there are routine periodic medical examinations to ensure continued fitness to the standards required for piloting, or other flight duties as appropriate. Thirdly, a medical examination is required after any sickness to ensure fitness, not merely for ordinary work such as might be assessed by the National Health Service doctor, but for the particular requirements of aviation. A further very important aspect of work of the flying staff medical officers is the personal interview with those who require advice or help on psychological matters, which can seriously affect a man's judgment and therefore his fitness for flying duties.

Experience is an invaluable asset of a medical officer in this connexion. In B.O.A.C. there has been built up over the years a very close rapport between flying staff and the medical officers looking after them, whom they have come to regard as friends and advisers. An appreciable portion of flying staff medical officers' time is taken up with flying down the routes, for only in this way can they fully appreciate the conditions under which the staff operate, and by living and working with the staff get to know their problems at first hand.

Overseas Staff

B.O.A.C. staff and their families are scattered all over the world, some in relatively large communities of several hundred and others relatively isolated. The expatriates return to the U.K. at least once in two years. They and their families then receive a complete medical overhaul. This is conducted by the overseas staff medical officer, who acts as the "family doctor" in more ways than one. He knows them and their families intimately, and refreshes his knowledge of their living conditions by periodic visits to overseas stations. All countries in the world are not as healthy as our own, and the conditions under which ground staff and their families live overseas may have a profound bearing on their health. Building design, mosquito control, dietary supplements, recreational facilities such as swimming-pools and tennis courts, air-conditioning, and so on are all matters on which the advice of the Branch is continuously sought.

Tropical Medicine

By virtue of B.O.A.C.'s world-wide coverage a substantial proportion of the illnesses flying and ground staff are subject to are of a tropical nature, among which the dysenteries and malaria loom large. Advice on preventive and remedial measures in this connexion is one of the responsibilities of the senior medical officer (ground), who, apart from being specially qualified in this subject, has spent many years of his professional life in the tropics. Such measures include supervision of food preparation and handling of water supplies, the hygiene of premises used by staff and passengers, and instructions on the use of antimalarial and other prophylactic drugs.

Industrial Medicine

The Corporation employs some 12,000 industrial staff in processes associated with aircraft, including the use of electrical and *x*-ray equipment, special paints, resins, and finishes, metal cleansing processes, metal plating, etc.

The study of industrial processes used in maintenance workshops, in the hangars, and on the aprons is the major responsibility of the industrial medical officer, and he is assisted in this work by the medical officer, industrial health unit, and the industrial health engineer, and at B.O.A.C.'s engine repair and overhaul factory at Treforest in South Wales by a part-time medical officer. Many of the processes developed to make overhaul work more efficient can, by reason of toxicity to the skin, the production of hazardous fume, ionizing radiation, and so on, be dangerous to the worker if not properly controlled. The Factories Acts lay down stringent regulations for some of these processes, but in many cases their proper control is a matter for discussion between the industrial medical officer and the production manager.

In the same way, working methods, if uncontrolled, can jeopardize the physical well-being of the worker. It is the industrial medical officer's responsibility to take note of all working methods, to assess the possible hazards, to devise protective measures against these hazards, and to secure their adoption by discussion and liaison with the production manager and the heads of other branches. An extensive programme of hearing conservation has recently been initiated for all staff whose duties may bring them in proximity to active jet engines. This includes audiometry and advice on appropriate protective measures.

To ensure that the preventive aspect of the industrial medical officer's work is given adequate backing, possession of the Industrial Nursing Certificate has been for some years an essential qualification for newly recruited nursing sisters.

Premises hygiene is the responsibility of the industrial medical officer in the case of London Airport; of the medical officers in charge at our Engine Overhaul Factories, Treforest, South Wales, and at Airways Terminal, London; and of the senior medical officer (ground) in the case of premises overseas. In the latter case, of course, the local manager acts on his behalf. Passenger restaurants, staff canteens, kitchens, changing and locker rooms, toilets, and so on are continuously under inspection to ensure that good housekeeping prevails. Much of this inspection work is carried out by the Corporation's hygiene officer, a fully qualified public health inspector.

Dentistry

B.O.A.C. employs three full-time dentists whose services are much in demand, the order of priority of treatment being emergencies, flying staff going on service, overseas staff during leave periods, and routine attention for ground staff. The time, trouble, and expense involved when a member of an aircraft crew is suddenly incapacitated by toothache can be imagined. Furthermore, it is often very difficult for aircrew, uncertain of their future time-tables, to keep dental appointments with private practitioners. Equally, it is difficult for expatriate staff and their families, during their short stay in the U.K., to arrange dental appointments under the National Health Service.

The Corporation is able to reclaim fees for dentistry from the National Health Service and from the individual patient, and, of course, there is a considerable reduction in lost working time by having the service available on the airport.

Applied Aeromedical Research

Advice to the management on the applications of aeromedical research is the direct responsibility of the

director of personnel and medical services, who is chairman of the Aircraft Safety Requirements Committee and a member of the Air Safety Committee. He is assisted by the research medical officer, who is a fully qualified pilot and maintains close liaison with the R.A.F. Institute of Aviation Medicine at Farnborough, with overseas research workers, and with our own Flight Operations and Engineering and Maintenance Departments. By these means, and by flying on training and proving flights, he is able to keep abreast of all advances in this branch of knowledge, to apply these advances to Corporation practice, and to carry out experimental work suggested by conditions found on Corporation aircraft. Problems of oxygen presentation, air-conditioning and pressurization, lighting and layout of cockpit instruments, flight time limitations, cockpit environment, emergencies and first-aid in the air, survival, etc., require constant investigation, and new research is already in train in connexion with anticipated supersonic airliners of the future.

It might be argued that other outside agencies should be utilized to cover this function, but this is not practicable. First, even if an outside agency could be persuaded to undertake some specific investigation, a considerable time might elapse before a report was forthcoming. Secondly, the problems requiring investigation are peculiar to civil aviation and it would not be easy to find an organization with the time or facilities to carry out the particular investigations required. Thirdly, while the closest possible liaison is maintained with the R.A.F. Institute of Aviation Medicine at Farnborough, many of the problems of civil and military aviation are widely divergent, and, understandably, the R.A.F. cannot devote time and money to problems which are specifically civilian.

Moreover, since B.O.A.C. is the British Government's "chosen instrument" for the carriage of long-distance air traffic, it seems reasonable that it should be an acknowledged leader in the advance of knowledge.

Instruction

It is vital for their own safety and well-being, and for the health and comfort of their passengers, that flying staff should have some knowledge of aviation medicine, first-aid, and hygiene. The senior medical officer (air), who is himself an ex-pilot, is in charge of this instruction and is assisted therein by the research medical officer, the hygiene officer, and the medical supplies officer. The lectures given cover the effects of altitude and decreased barometric pressure, the use of oxygen, care of the ears, aircraft pressurization, survival and rescue, first-aid, personal hygiene in the tropics and elsewhere, and food-handling hygiene.

Hygiene and Sanitation

The hygienic state of our aircraft is a matter of great importance and is the responsibility of the senior medical officer (air). The Corporation's hygiene officer assists him by making regular inspections and carrying out appropriate tests. Apart from ordinary cleanliness, the type of disintegrating and disinfectant fluid used in aircraft toilets must be considered, as also the technique and material used to keep aircraft free from insect pests which it may have acquired as stowaways *en route*.

The water which an aircraft carries for its passengers' needs must be replenished at every stop, and at many airports the mains supply is far from pure. To overcome this, the hygiene officer has devised a system whereby all water loaded on to our aircraft is chloraminated, the technique being that water is drawn from the mains into a bowser (which is regularly cleansed) and is therein treated with chloramine T three to four hours before the aircraft is to be serviced. From the bowser the water is pumped into the aircraft tanks. The tanks are cleansed and sterilized at regular intervals. Constant bacteriological checks are made to ensure that the correct procedure is being followed and that it is effective.

Food for the aircraft's passengers has to be taken, and over the years aircraft catering has come to be almost a major industry. Like any branch of catering, however, strict hygiene control is necessary and the hygiene officer is responsible for a continuous process of inspection, sampling, and testing. In the majority of instances the food is pre-cooked, quickly cooled, enclosed in aluminium-foil containers, and deep-frozen. On delivery to the aircraft the food is still in the frozen state; it is then thawed and reheated in the aircraft's ovens. Quality of materials, kitchen hygiene, cooling conditions, and refrigeration efficiency are all matters of vital importance and require constant supervision, not only in B.O.A.C.'s own Aircraft Catering Unit at London Airport, where some 3,000 meals a day are prepared, but in many smaller units all over the world. Frequent bacteriological checking is necessary. These aircraft catering units not only supply the food to the aircraft but also provide clean crockery, glassware, and cutlery in exchange for the dirty equipment taken off the aircraft. Washing-up techniques have therefore to be carefully checked to avoid clean food being served on bacteriologically dirty plates.

Ancillary Services

First-aid and Nursing.—Even the healthiest of individuals cannot remain healthy all the time and accidents are always liable to happen. A first-aid service for employees is therefore a necessity. At London Airport there are five strategically placed medical units manned by nursing sisters assisted by medical orderlies; there are two at Treforest and one in London. The nursing staff—21 nursing sisters and 12 medical orderlies—are the responsibility of the matron, working in conjunction with the industrial medical officer. First-aid treatment for accidents and minor ailments is given, and many employees are referred back by their family doctors for continuation treatment if their condition does not require them to stay away from work. An average yearly total of 83,000 attendances at the units is made by the staff. This is apart from attendances for routine examinations. First-aid treatment of passengers on our aircraft is administered by the stewardesses, all of whom are given a basic training in first-aid and have at their disposal a comprehensive first-aid outfit. An appreciable proportion of stewardesses are State-registered nurses. In addition to the provision of first-aid treatment, the nursing staff are responsible for the disinsectization of aircraft and for the handling of invalid passengers.

Therapeutic Services.—In many cases of illness or disability after an accident the employee may require special types of treatment although he is not incapacitated. Without special facilities he must stay at home or absent himself from work for several hours at a time. Much of this absenteeism is now unnecessary,

since the Corporation provides physiotherapy, controlled by the industrial medical officer. An *x*-ray unit, audiometric unit, and pathological laboratory have also greatly improved the service which medical officers can offer to the staff. A consultant radiologist visits the department twice weekly. Shortly it is anticipated that ophthalmic and skin clinics attended by consultant specialists will also be made available, as well as the services of a visiting chiropodist. The benefits derived are impossible to assess financially, for, although it may be possible to demonstrate a reduction in lost working time, much of the benefit is in the form of staff contentment and confidence in the knowledge that their medical needs are fully met.

Domiciliary Treatment at Overseas Stations.—The benefits of the U.K. National Health Service are not available overseas, but the Corporation must still accept responsibility for the health of its employees and, in the case of expatriates, for their families. At each overseas station the senior medical officer (ground) is responsible for arrangements for doctors to be available for the treatment of both expatriates and locally engaged staff.

Medical Supplies.—Without supplies the Department could not work, and, in addition to drugs, etc., required by the medical officers and nursing staff, first-aid kits for aircraft and rescue dinghies, including special stretchers for invalid air travel, portable oxygen sets, etc., must be provided. Supplies are located at strategic points throughout the world to deal with emergencies and replenishments, this being the responsibility of the medical supplies officer and his staff, who also do the purchasing for the Department.

Statistics and Records.—Accurate statistics of sickness and injuries among staff are essential in order that realistic advice can be given to the management and the board regarding employment policy. Relief arrangements, length of tours, leave allowance, type of housing provided, and so on may be dependent on these statistics. Accident statistics may highlight some particular work situation where extra safety precautions are advisable. Information is also needed on occupational breakdown in flying staff and sickness by aircraft type or route flown. The Corporation's doctors would be working in the dark if they did not have comprehensive medical records of all employees: these, of course, have to be kept continuously up to date, so that no matter which doctor examines the particular individual he will have an accurate picture of the medical history. Over 20,000 medical records, including those of employees of associated companies and other organizations for whom we act, are maintained.

Invalid Passengers

B.O.A.C. carries many more declared invalid passengers than any other airline in the world, the numbers having increased from 144 in 1950 to over 4,000 in 1960. This is a highly specialized procedure, based on knowledge which has been built up over the years. When private practitioners or hospitals have a patient they wish to be transported by air they get in touch with the senior medical officer (air) and advise him of the nature and extent of the illness. He in turn sends them a questionary requiring specific details. On receipt of this the doctor is advised whether or not the person may travel, and, if the answer is in the affirmative, what special precautions or assistance may be required *en route*. This may include provision of an attendant, administration of drugs, oxygen and other equipment, or a specially arranged berth or stretcher. When an invalid passenger has been accepted, detailed signals are sent to all stations *en route* for the provision of the necessary attention where required, including being met by doctors, nurses, or ambulances where appropriate.

A medical unit, staffed by nursing sisters on a 24-hour basis, is maintained in close proximity to the passenger-handling area at London Airport, and through this unit the great majority of our invalids pass. Bedrooms are available to take care of those who may have a wait of several hours between sections of their flight, for mothers with young children, and for departing and arriving passengers whose ambulance journey to or from the airport may not conveniently coincide with the timing of the aircraft. In addition to the duties entailed in seeing patients on and off the aircraft and caring for them in the unit, the nursing sisters arrange emergency vaccinations for passengers who are found to have incomplete documents and provide a first-aid service both for passengers and for the staff working in the vicinity.

A good deal of specialized equipment for the handling of invalid passengers has been developed by the medical supplies officer, much of it to his own design, and other airlines often hire this equipment from us for use on their own aircraft.

Immunization of Passengers and Staff

Passengers travelling on international airlines are required by the governments of the various countries visited or transited to be vaccinated against such diseases as smallpox, yellow fever, cholera, and, in some cases, plague and typhus. It is not always easy for busy people to satisfy the regulations, therefore the Corporation maintains an immunization clinic at Airways Terminal, Victoria, London S.W.1, to assist them. This is the responsibility of the immunization medical officer, who carries out over 12,000 vaccinations a year. The Corporation makes a charge for this service and the clinic is fully self-supporting.

Flying staff, overseas staff and their families, and members of the U.K. staff who are required to travel on duty receive their vaccinations chiefly at the medical headquarters building at London Airport, where a further 9,000 vaccinations are given annually.

Liaison with Other Organizations

With a world-wide organization like B.O.A.C. it is essential that there should be liaison with others interested in similar fields, and this applies to Government medical departments and organizations such as the Air Transport Association, Aerospace Medical Association, Airline Medical Directors' Association, the World Health Organization, the Association of Industrial Medical Officers, Industrial Welfare Society, the Flying Personnel Research Committee, R.A.F. Institute of Aviation Medicine, and so on. The director of personnel and medical services is responsible for this liaison.

Conclusion

This article has indicated that many facets of the medical organization of an international air-transport carrier, including the highly specialized aspects of

high-altitude flying, the industrial processes associated with aircraft maintenance, the geographical and immunological problems, and the widespread 24-hour cover required.

Inevitably there is a certain degree of overlapping of duties, and it would be difficult to think of any important aspect of the work which is not of interest to almost every medical employee. To ensure that all senior employees—that is, doctors, dentists, matron, medical supplies officer, hygiene officer, and industrial health engineer—are fully conversant with what goes on, a monthly meeting is held to discuss difficulties, decide policy, and distribute information. The aim of the service is to provide for every employee the maximum possible guarantee against sickness or injury, the best chance of a speedy recovery by the provision of adequate immediate treatment, and such after-treatment as will enable him to be away from his work for the minimum time.

I am grateful to Dr. K. P. Hare for help in the preparation of this article and Dr. A. S. R. Peffers for his valuable comments.

HOSPITAL AND MEDICAL SCHOOL DESIGN

INTERNATIONAL SYMPOSIUM IN DUNDEE

A closed international symposium on "Hospital and Medical School Design" was held at Queen's College, Dundee, from July 12 to 15, under the chairmanship of Principal Sir MALCOLM KNOX. On the first day the main discussion centred on the analyses of the design of three, widely separate, British medical schools—St. Thomas's Hospital in London, the University Hospital of Wales in Cardiff, and the Ninewells Hospital and Medical School in Dundee—though two American schools were also described (Stanford Medical School and the University of Washington Medical Center in Seattle). On the second day the design of a clinical research centre was the main topic, with Professor J. R. SQUIRE, the director designate of the Medical Research Council's projected clinical centre at Harrow, as the opener of the discussion. Later in the meeting special facets of the medical school design, such as "teaching out-patient departments" and the design of ward units, were debated, the three British schools whose plans had already been anatomized serving as examples.

We are indebted to several correspondents for the account which follows. The section on ward units is by an architect. The proceedings will be published in full.

St. Thomas's Hospital

Mr. G. H. BATEMAN, chairman of the hospital's medical advisory panel, described the procedure and progress of the planning organization and negotiations that had taken place, not only within St. Thomas's during the past 17 years, but also with the many outside authorities, and of the exceptional difficulties arising from the hospital's site opposite the Houses of Parliament. He emphasized the importance of the medical staff delegating to a small number of their colleagues authority to advise the governors on all medical aspects of rebuilding, and the advantage derived from having a senior and experienced member of the hospital's administrative staff responsible for co-ordinating all the administrative problems. The dean, Mr. R. W. NEVIN, described the provision being made in the new hospital for student teaching. There would be close and convenient access between the main hospital block, the residential quarters for medical staff, and the premedical and preclinical school buildings.

Mr. W. F. HOWITT, architect, said that the principal limiting factors were the restricted site (some 16 acres), planning limitations due to the hospital's situation, the need to keep the existing hospital running without undue interference, and the need to build the new hospital in stages. He referred to the revisions of the plans necessitated by the change of policy from reconstruction of existing buildings to complete rebuilding. He also described the preliminary action, now completed and taken at the expense of the Hospital's Endowment, to provide an enlarged and undivided site. This had involved the diversion of Lambeth Palace Road, the acquisition of extra land, partly from the garden of Lambeth Palace, and a large rehousing scheme. Work on the first stage of rebuilding would, it was hoped, start in September.

Mr. W. A. A. PEARSON, deputy clerk to the governors, described the basis on which the wards and out-patient departments had been planned. In view of the importance of the ward design the governors had carried out experiments in the existing wards to test different arrangements of beds, and had decided upon a T-shaped ward containing 28 beds, four of which would be in single rooms and the remainder in bays containing four beds each. The ward plan had largely determined the shape and size of the new hospital. The total bed complement of approximately 820 would be in 32 wards. The main 12-story ward block will be linked on the lower four floors to an adjoining building containing stores and supply departments, out-patient departments on two floors, and 12 main operating theatres.

University Hospital of Wales

Dr. D. G. MORGAN, secretary of the board of governors, described the history of the scheme for providing in Cardiff a teaching centre which would contain 800 beds with an entry of 80 medical and 50 dental students. Dr. TREVOR JONES, provost of the medical school, then explained how the idea of integrating school and hospital had come to be accepted. For many years school and teaching departments had been improvised in existing hospitals, and the close relationship of academic work with care of patients was therefore very familiar. Professorial units had been a feature of the medical school in Cardiff, so that much of the teaching in clinical medicine was organized along the lines of a university department, parallel and complementary to the contributions made by hospital staff, who had the full use of the units. The aim had been to bring together the three functions of a medical teaching centre—teaching, research, and clinical care—by means of an architectural expression. The team at Cardiff, which had worked very closely with the architects, realized that there was scope for experiment, for diversity, and even for nonconformity.

Mr. G. R. FINDLATER, architect, said they had found that the site contours had been helpful in permitting entrances at three floors, and the planning of a 10-story building had presented no difficulty. A quadrangular plan had been adopted; the main communications were on a north–south axis with the important integration of academic accommodation along the east–west axis and with links to all departments. The requirements of flexibility and the possibility of extension had to be combined with a relatively compact design. These points were illustrated with slides of diagrammatic plans and other plans, which showed how the site of 53 acres had been developed to provide two contrasting areas.

Professor HAROLD SCARBOROUGH, describing the facilities for teaching students, said that it was intended to provide for practically all undergraduate instruction to be available at one site and for residential accommodation to be provided for as many as possible of the students. The majority of the teaching departments were to be grouped around a large central library and were to be within easy reach of the wards, which themselves would contain rooms for study and laboratory work. Mr. D. HUGH JENKINS, consultant surgeon, said the standard ward was to contain 32 beds, and was planned as a duplex unit to accommodate both sexes, with the obvious advantage in flexibility, each half containing an eight-bedded ward, a four-bedded ward, and four single rooms. The units were arranged in groups of three, vertically stacked on seven floors. The out-patient departments were grouped on the main ground floor and planned in ten suites, seven of which were of standard design.

Dundee Medical Centre

For the Ninewells teaching hospital at Dundee there is a magnificent site of 200 acres, overlooking the River Tay and the Firth of Tay. The hospital is to have 700 beds covering general medicine, surgery, and other specialties, and facilities are being provided for an annual intake of 65 students in their clinical years of study and for postgraduate instruction and research.

Professor R. B. HUNTER, dean of the faculty, said that the keynote of policy had been the concept of embedding the medical school in the hospital. The medical school and hospital had been planned as a single entity. He emphasized that it was of great value to have investigational studies and diagrams prepared by the architect during the preparation of the brief.

Professor ROBERT MATTHEW, architect, stressed the value of a small planning team representing the client and including the architect. The early appointment of the architect and consulting services engineer was a prerequisite to successful planning. Dundee had been fortunate in its site, and because of this he had been able to put forward a design in which a low and horizontal development was possible. The basis of the scheme was a five-story central block with the medical school to the east of the block and the hospital to the west and south of the central block (see Fig. 1). The principle of "embedding" had been largely achieved, in that the professorial units were across the corridor from the professorial wards. The general concept of the architectural layout was horizontal development—planning of accommodation in depth and the placing of closely linked departments on the same level.

Dr. T. SOMMERVILLE said they were providing facilities to cover teaching in the paraclinical and clinical subjects. Special features included a demonstration and a tutorial room in each ward unit, examination rooms for students in the out-patient suites, a central exhibition suite for co-ordinated demonstrations by different departments, and a large reading room in the library for the students. Professor D. M. DOUGLAS dealt with the general principles of operating-theatre design, stressing the need for the zoning of the theatre. He recommended that clean, sterile, and disposable zones, with architectural barriers between them, should be constructed. Reception and recovery wards, supervised by specially trained nursing staff, were included in the plan for the operating suite. The proposal was that general clinical control of these two ward units should rest with the anaesthetists.

In the general discussion, the question of the provision of research facilities for part-time consultants in the employment of regional boards was raised. Dame JANET VAUGHAN noted that Dundee had made provision for part-time consultants in their plan and expressed her approval of this feature. She also thought that the question of providing hostel accommodation for patients needed urgent examination. One of the trends in modern medicine was the examination of patients in the out-patient department, but that sometimes made it necessary for such a patient to spend a night in hospital.

Comparison of Ward Units

[BY AN ARCHITECT]

The ward units of these three teaching hospitals all differ in size, all have some teaching accommodation on the ward, and, despite considerable variations in layout, all have adopted the T-shaped plan (see Figs. 2–4). The explanation of the plan shape is primarily because the units are to cater for both sexes, one-half male, the other female—that is, the duplex arrangement. All three designs are based on a high degree of centralized service (sterile supplies, linen, pharmacy, dishwashing, etc.).

St. Thomas's

The ward unit (Fig. 2) consists of 28 beds, four of which will be in single rooms. The remainder are in four-bed bays. The traditional teaching round of up to 20 students has been retained, but there is a small room (300 sq. ft.) shared by students and medical staff which can also be used for demonstration of patients. Three characteristics of the layout will be noticed: (1) The day-space is split into two parts, each of about 200 sq. ft., each part grouped with the bathrooms at the proximal end of the ward. (2) The nurses' station and the two treatment rooms are placed in the centre of the ward. (3) The clinical staff (head of unit, registrars, house-officers) all share one room on the unit.

The two treatment rooms are mechanically ventilated, and mechanical ventilation is provided in the general ward area to ensure a minimum rate of air change when it is necessary to keep the windows closed (high winds, very cold weather, fog, etc.). The ward units are grouped as a series of four T-shaped towers joined together in a 12-story slab block containing a total of 827 beds. Vertical access to each unit is in the stem of each T; a total of six lifts per tower are provided for this purpose. An unusual feature of the ward block is the embedding of laboratories and animal rooms on the fourth and seventh floors; presumably provision for their expansion is made elsewhere.

Cardiff

The ward unit (Fig. 3) contains 32 beds, eight of which are in single rooms. There are two eight-bed rooms and two four-bed rooms. There will be no teaching rounds,

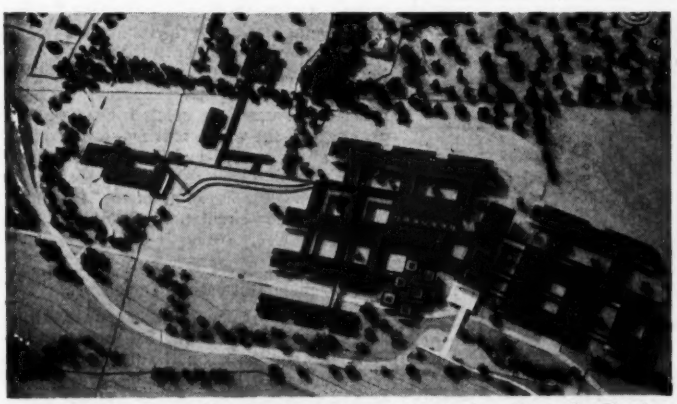
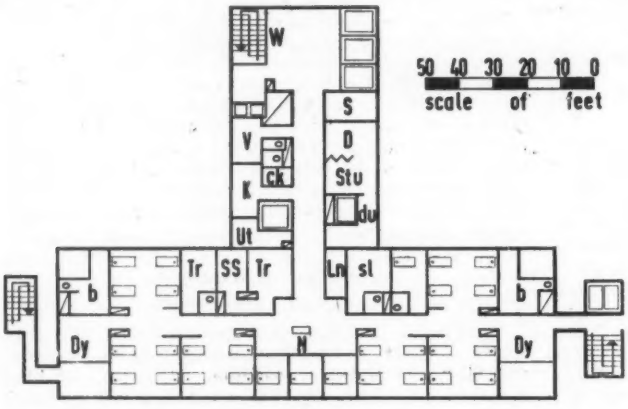


FIG. 1.—Model of teaching hospital and medical school at Ninewells, Dundee, from the north. The wards are on the southern exposure. The medical school is to the west of the main concourse block.

a demonstration room (250 sq. ft.) being provided for clinical teaching in the stem of the T. The more important characteristics are: (1) There is a nurses' station placed in the centre of each half of the bed area, with one treatment room for the whole unit. (2) The day-space (440 sq. ft.) is concentrated at the centre of the unit and is intended to be capable of division into two halves by a folding partition.

Like the St. Thomas's scheme, the ward units are grouped as a series of T-shaped towers (three in number), joined together in a 10-story slab block containing a total of 800 beds. Unlike St. Thomas's, however, it is possible to move from one unit to the adjacent one by a main corridor linking the entrances to each unit. A surprising feature of the vertical circulation is the provision of two bed-sized lifts in the middle of the bed area, where a foyer with reception desk is provided. The clinical departments are in a corresponding 10-story block, parallel to the ward block.



Key

al	Air lock	Ex	Examination room	N	Nursing station
b	Bathroom	f	Female lavatories	Re	Reception
C	Consultant	H	Head of unit	S	Sister
Dm	Demonstration room	HO	House officer	sl	Sluice room
ds	Disposal room	Iv	Interview room	SR	Senior registrar
dt	Dirty treatment room	K	Kitchen	Tr	Treatment
du	Dirty utility	lb	Laboratory	Tu	Tutorial
dy	Day space	ln	Linen store	W	Waiting area
eq	Equipment room	m	Male lavatories		

FIG. 2.—Standard ward unit at St. Thomas's Hospital.

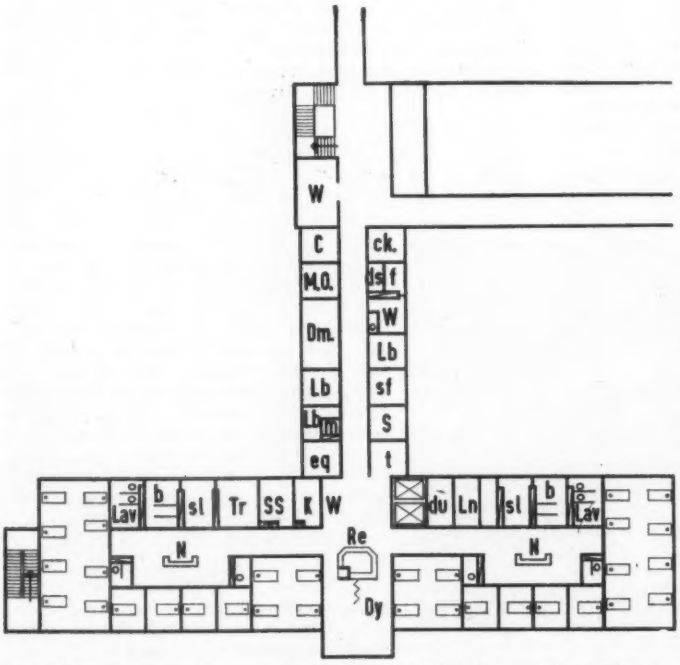


FIG. 3.—Standard ward unit at University Hospital of Wales. (See key to Fig. 2.)

Dundee

The ward unit (Fig. 4) at Ninewells is of 48 beds, 12 of which are in single rooms, the remainder in six-bed bays. There will be no teaching rounds, and visual observation of a high proportion of the beds is required. Teaching will be done in a demonstration room (400 sq. ft.) and a tutorial room (200 sq. ft.) on each ward unit. The latter room will be fitted up for simple laboratory work by the student.

Two immediate impressions strike one in studying this design: (1) The compact planning of the bed area by means of a central core of utility and bathroom accommodation. (2) The treatment room and nursing station are at the extreme end of each ward on the unit.

The unit is based on a concept of zoning in which the progressive stages of care, from the seriously ill at the acute end to the convalescent at the recovery end, are reflected in the layout. Three characteristics of this layout may be noted: (1) The "acute" zone of each ward is further from the major traffic movements of the entrance. (2) The nursing station, clean utility, treatment room are grouped at the focal point of the acute zone. (3) The "recovery" zone of each ward adjoins the central day space of the unit. Such a grouping of the day space (some 800 sq. ft.) is an attempt to recognize the influence of early ambulation on ward design. In the Ninewells unit the total day-space is divided into two quiet rooms, one male, one female, with a common social room.

Adaptability in the use of this layout can be provided in two ways: (*a*) To meet variations in sex distribution within the specialty: by using the single rooms it is possible to allocate 30 out of the 48 beds on the ward unit to one sex. (*b*) To meet variations in demand for beds within the one specialty: by overflowing into an adjacent ward unit. This latter point illustrates another feature of the Ninewells design—the horizontal grouping of closely linked functional units. This governs the grouping of the ward units in two respects: (1) All similar ward units are on the same level—for example, all surgical wards. (2) The ward units are on the same level as their respective clinical departments. This general concept of horizontal grouping has created the essential character of the whole scheme—a predominantly low group of buildings. The ward blocks are of three stories and are linked together by the hospital street, the main spine of the circulation system of the scheme.

"Teaching Out-patient Departments"

All three schemes had in common a number of basic planning features; in each there was emphasis on the need for access on ground-floor level to the out-patient department, on the separation of out-patient traffic from in-patient traffic, on convenience of access from the out-patient depart-

ment to the wards, on close association with the diagnostic and therapeutic departments, without prejudice to the relationship between those departments and the in-patient accommodation, and on the need for a measure of standardization in the out-patient clinic accommodation. There were, nevertheless, some notable differences in the designs interpreting these features, some perhaps imposed by building and site restrictions, and others possibly the consequence of a difference in emphasis and outlook by the planning teams.

In the Cardiff and St. Thomas's schemes a limited number of clinics were located in the floor immediately above the main out-patient department, while in the Dundee scheme the casualty department, including the out-patient theatres, was on the floor below. In all three, however, there was convenience of access to these areas without interference with in-patient traffic. The separation of out-patient and in-patient traffic was well achieved in each case, and good relationships had been obtained with the radiology and physiotherapy departments. It was notable in the Cardiff and Dundee schemes that small detached diagnostic laboratories had been located in the out-patient department area, connected with the main pathology laboratories by pneumatic tube for the purpose of more advanced investigations.

There was some variety in the extent to which the clinic accommodation had been standardized. In the Dundee scheme each clinic had its own treatment room, and, partly for this reason, specially designed clinics have been provided for ear, nose, and throat surgery and ophthalmology, and a modified standard clinic for dermatology. In the Cardiff scheme, on the other hand, a central treatment room was provided for use in common by all the out-patient suites, and this permitted a greater degree of standardization of suite accommodation than was achieved in the Dundee scheme. The designs for all three schemes were based on moderately deep planning, with a varying degree of reliance on artificial lighting and mechanical ventilation. In no case, however, was this type of design carried to the extent that it has been in a number of recent American schemes, such as the University of Washington Medical Center in Seattle, where there is almost complete dependence on artificial light and mechanical ventilation.

The topic was "teaching out-patient departments," and it was interesting to find differences on the solutions offered to the problem of teaching undergraduates in the out-patient department. From the designs exhibited, it seemed that group teaching was expected to be a feature of the system in both Cardiff and St. Thomas's. In the Dundee scheme, on the other hand, very limited provision was made for group demonstrations in the out-patient department, the emphasis being rather on a marked limitation in the number of students present with a patient at any time.

Clinical Research Centre

Dr. J. MASUR, from Bethesda, U.S.A., discussed the design and organization of a clinical research centre, with particular reference to the facilities provided for this purpose at the National Institutes of Health in Bethesda. The central structure there was a 14-story, air-conditioned building, designed and constructed in 1948–52, which provided 500 beds and 1,100 laboratories for the integrated laboratory and clinical investigational programmes in cancer, heart disease, mental illness, arthritis and metabolic diseases, neurological diseases, allergic and infectious diseases, and dental diseases. The basic design afforded proximity of laboratory and patient-care staffs to permit free interchange of ideas and knowledge.

The central stem of the hospital laboratory building was a modified two-corridor plan with rooms for patients on the south side, nursing services in the middle, and laboratories for special clinical investigations and offices on the north side. A typical nursing unit contained 13 two-bed rooms. The typical patient's room accommodated two beds and had its own bathroom, wash-basin, and clothes closet: the room was equipped with nurse-call intercommunication and with outlets for oxygen, vacuum, electricity, telephone, radio, and television. The laboratory wings were designed on 12-ft. modules, with utility service lines in vertical risers in outside walls. Metal demountable partitions and standardized laboratory benches and furniture made the individual areas readily interchangeable as animal rooms, offices, and laboratory units.

Professor J. R. SQUIRE, in opening the discussion, said that the concept of a clinical research centre should no longer be regarded as exceptional but the standard pattern for the future. Laboratory aids were a necessary part of clinical diagnosis. The bulk of research in the future was likely to be conducted in our regional board hospitals. He was feeling his way in his thinking on the ratio of area for beds to that for laboratories. He suggested that in regional board hospitals the bed area should be twice the laboratory area, in a teaching hospital it should be of the same size as the laboratory area, and in a clinical research centre it should be half that of the laboratory area.

Professor J. MCMICHAEL considered that Bethesda was fortunate in that in the U.S.A. research was venerated and there was the additional attraction of free treatment for the patient in order to save fees, which were heavy in the United States. He said that the Hammersmith project had been started 25 years ago. The basic idea was that patients would be transferred to the Postgraduate School from the 200,000 beds which were available in the London County Council hospitals. This had not worked, because cases were not referred, and in consequence the hospital had

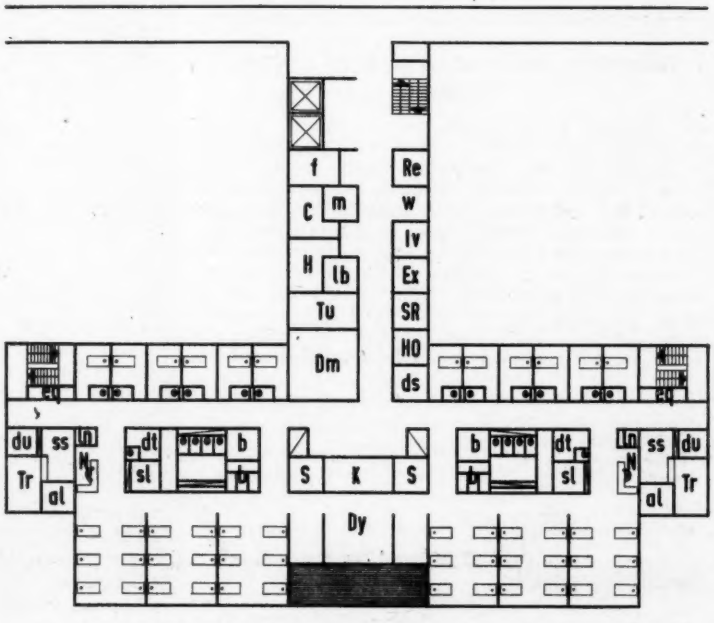


FIG. 4.—Standard ward unit at Dundee Medical Centre. (See key to Fig. 2.)

had to provide a local service in order to obtain sufficient clinical material to meet teaching and research needs. Dr. MASUR said in reply that they had never had any trouble over the lack of patients for investigation in research programmes.

APPROVED NAMES

The last supplement to the consolidated list of "approved names" was published in the *Journal* of May 27 (p. 1535). A new supplement, dated July, 1961, is printed below. Communications relating to "approved names" should be addressed to the Secretary, British Pharmacopoeia Commission, General Medical Council, 44 Hallam Street, London W.1.

Approved Name	Other Names	Notes
Bamipine	4-(*N*-Benzylanilino)-1-methylpiperidine "Soventol"	Treatment of pruritic and allergic conditions
Bucetin	*N*-β-Hydroxybutyryl-*p*-phenetidine	Analgesic
Chlorphentermine	4-Chloro-αα-dimethylphenethylamine "Lucofen" is the hydrochloride	Appetite suppressant
Diethadione	5:5-Diethyloxazolidine-2:4-dione	Analeptic
Halethazole	5-Chloro-2-(*p*-2-diethylaminoethoxyphenyl)-benzothiazole "Episol"	Fungicide
Halquinol	A mixture of the chlorinated products of 8-hydroxyquinoline containing about 65% of 5:7-dichloro-8-hydroxyquinoline "Quixalin"	Treatment of bacillary dysentery
Laurolinium acetate	4-Amino-1-dodecylquinaldinium acetate "Laurodin"	Antiseptic
Lynoestrenol	17α-Ethynyloestr-4-en-17β-ol "Orgametril"	Suppressor of ovulation
Paramethasone	6α-Fluoro-11β:17α:21-trihydroxy-16α-methylpregna-1:4-diene-3:20-dione 6α-Fluoro-16α-methylprednisolone "Haldrone" is the 21-acetate	Adrenocortical steroid
Thenyldiamine	*N'N'*-Dimethyl-*N*-2-pyridyl-*N*-3-thenyl-ethylenediamine	Antihistamine
Tigloidine	Tiglyl*pseudo*tropeine	Relief of muscular spasticity

New Appliances

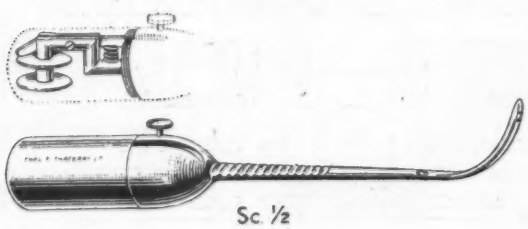
A MODIFIED CONTINUOUS-FEED ANEURYSM NEEDLE

Mr. ANTHONY R. ANSCOMBE, surgeon, Royal Infirmary, Manchester, writes: Many surgeons use an aneurysm needle for ligation, but one disadvantage of this method is the repeated need to rethread the needle and the consequent waste of time and movement. Tibbs (1952) described a new type of aneurysm needle designed to eliminate the defect. The handle of the instrument was enlarged to contain a reel of suture material, and pulling on the thread provided a continuous flow as required. When a knot was tied the run of the suture material was stopped by firm pressure of the thumb or index finger of the hand holding the instrument. If many ties are made at short intervals, as in ligation around the greater curvature of the stomach, this need for firm pressure can be tiring.

The instrument has therefore been modified and a friction device has been incorporated in the handle to control the run of the reel. The suture material will run only when the friction device is released by pressure on a stud so placed as to lie opposite the natural position of the thumb when the instrument is held in the hand. Knots can then be securely tied against the hold of the friction device with no extra fatigue, and the instrument can be held permanently in the hand until all vessels needing ligation have been dealt with.

Extra interchangeable reels are available so that the size of the ligature can be varied, and the mirror images of the instrument are made for use with the right or left hand.

The modified aneurysm needle has been made for me by Charles F. Thackray Ltd., of Leeds, to whom I am indebted for several prototypes of the instrument and for the illustration.



Sc. ½

REFERENCE

Tibbs, D. J. (1952). *Brit. med. J.*, **2**, 1201.

Nova et Vetera

SIR ALMROTH WRIGHT, 1861–1947

COMMEMORATIVE ADDRESS AT THE ROYAL ARMY MEDICAL COLLEGE

Almroth Edward Wright was born on August 10, 1861, and on August 10, 1961, Brigadier L. R. S. MACFARLANE, professor of pathology at the Royal Army Medical College, Millbank, gave an address in commemoration of this event. He began by remarking that Almroth Wright was born under the sign of Leo, and it was curious that in his characteristics and appearance he was often described as resembling a lion.

Having graduated B.A., with first-class honours and gold medal, in modern literature at Trinity College, Dublin, Wright took his medical degree at the same university soon afterwards, and then studied on the Continent before becoming a demonstrator of pathology at Cambridge. His abiding interest in haematology began at this time, and he was able to continue his research on the clotting of blood when he went out to Australia as a demonstrator in physiology at the University of Sydney.

Antityphoid Vaccination

In 1892, at the age of 31, he was appointed professor of pathology in the Army Medical School at Netley. He was not in the Army in this post, which, as Brigadier MacFarlane observed, may have been one of the Army's earliest experiments with "civilianization." Among other subjects Wright had to teach bacteriology, and he was soon immersed in research on vaccines. Malta fever was his first objective, and after vaccinating himself with killed organisms he then injected a live culture. The result was a "very miserable attack" of Malta fever. During his convalescence he began to think about preparing an antityphoid vaccine. Having completed laboratory tests, he had difficulty in obtaining human proof of his theories. He inoculated himself and other volunteers, including "surgeons on probation"—a procedure the War Office frowned on. But, as Brigadier MacFarlane observed, "his faithful colleagues submitted themselves as guinea-pigs and, although they

were very sick, they never succumbed to typhoid infection."

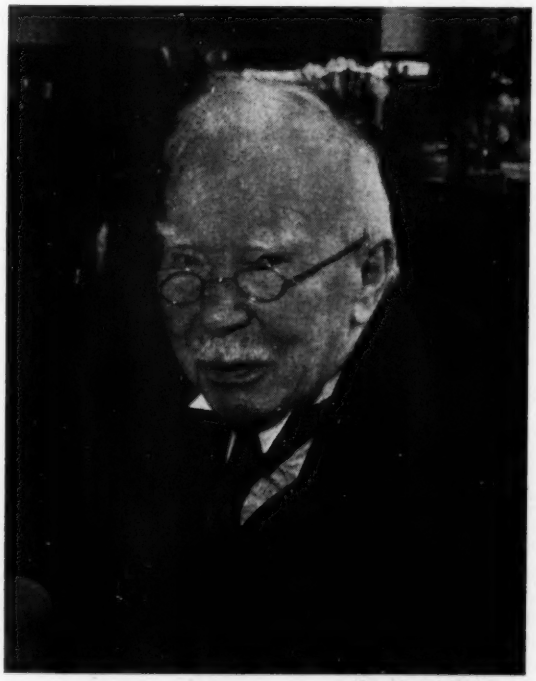
The outbreak of the South African war gave him his golden opportunity, though vaccination, then as now, was voluntary, and he had great difficulty in obtaining volunteers. After he left Netley his work was carried on by Leishman, and antityphoid vaccination was thus placed on a firm footing before the outbreak of the first world war. Just before the end of the century Wright went to India for the Plague Commission and there played an important part in the evolution of plague vaccine.

Wright's relations with the Army authorities were not always happy, but among the great majority of the officers with whom he worked he inspired loyalty and affection. In 1902 he was offered the post of pathologist at St. Mary's Hospital, and since the War Office would not agree to his holding this appointment and the chair of pathology at the Army Medical School, he left Netley.

At St. Mary's Wright continued with his antityphoid campaign and turned his attention to vaccine therapy over a wide range of conditions. "He was never known to use an attenuated or live culture for prophylactic vaccine purposes and steadfastly resisted B.C.G. almost to the end, stating that he would never be convinced until he could show or be shown that no killed culture could not do the job better."

Opsonic Era

This period of his life was the opsonic era. He postulated a substance in human serum acting on bacteria and rendering them liable to phagocytosis. Vaccination in his view raised the opsonic index of the patient's blood. His watchword was, "The physician of the future will be an immunizator." World-wide attention was shown in his work and he was knighted in 1906 and elected F.R.S. in the same year. It was not only medical men who were interested in Wright and his research, for George Bernard Shaw often visited him and they became friends. Shaw wrote the part of Sir Colenso Ridgeon, in *The Doctor's Dilemma*, around Wright, much to the latter's annoyance.



[*Press Portrait Bureau*
Sir Almroth Wright in 1940.

First World War

On the outbreak of the first world war Wright became a colonel in the Army Medical Services and established a laboratory in Boulogne, where he was joined by Alexander Fleming. Here they began their classic work on the sepsis of wounds, work which continued at St. Mary's after the war. His investigations included the "drawing power" of salt solutions on wounds. He advocated early suture and showed that serum inhibited the action of antiseptics.

Distressed at the manner of evacuation of the wounded, and at various faults in the medical administration, he wrote a famous memorandum advising the creation of a War Office Department of Intelligence and Investigation. This offended a good many senior officers, and Wright, in fact, was asked to resign by Sir Arthur Sloggett, D.M.S. in France, who withdrew his request on the advice of Lord Derby. But Wright's original idea finally came to fruition with the formation of the Consultants Committee in 1940 by Sir Alexander Hood.

Immune Therapy Versus Chemotherapy

Just before the war Wright became the first director of the department of bacteriology of the Medical Research Committee. When the war ended he gave up this work and confined himself to his work at the Institute at St. Mary's. For a time he was interested in his friend Paul Ehrlich's work on chemotherapy, but he abandoned his own researches in this field, convinced as he was that immune therapy would come into its own again. He was not even particularly impressed with the significance of Fleming's work on penicillin. But Fleming's name is now associated with Wright's in perpetuity in the Wright–Fleming Institute.

During his long life Wright was the author of 150 articles and books. He wrote a number of works on subjects unconnected with medicine, including *The Unexpurgated Case Against Woman Suffrage*. He was often thought to be a woman-hater, but, as Brigadier MacFarlane remarked, this was not so, "he simply liked them in their proper place."

Honours were heaped upon Sir Almroth Wright at home and abroad. During the first world war he was regarded with a reverence almost amounting to worship by French surgeons. He could never leave anything alone which offended or distressed him. Kind and patient with the young, the learner, the lame dog, he was ruthless in giving vent to his opinions when he felt that they were just, and especially when the object of his attack was of sufficient stature to hit back. "The Army authorities were by no means the only ones with whom he quarrelled," observed Brigadier MacFarlane.

In 1940 he had a severe operation for cholecystitis, but he continued going to the Institute at St. Mary's until the end of the second world war. Eventually he retired to his home and beloved garden at Farnham Common, dying there peacefully a few weeks later.

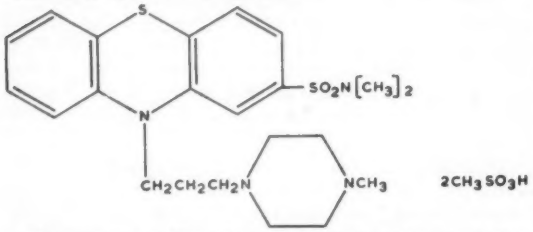
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Thioproperazine

"Majeptil" (May and Baker).

Chemistry.—Thioproperazine is 2-dimethylsulphamoyl-10-(3-4'-methyl-1'-piperazinyl propyl) phenothiazine. It is issued for clinical use as the dimethanesulphonate, which contains 69.8% of the active base.



Pharmacology.—The effects of thioproperazine are similar to those of chlorpromazine, trifluopromazine, and prochlorperazine. Compared with chlorpromazine, it is a weaker antagonist of adrenaline, noradrenaline, and 5-hydroxytryptamine, and it shows lower sedative, hypotensive, and hypothermic activity. It has comparable antihistaminic action, but it is a much more potent anti-emetic substance and is more effective in inducing cataleptic states in animals.

Therapy.—The drug is supplied in tablets of 1 mg., 5 mg., 10 mg., and 25 mg. Ampoules of 1 ml. containing 0.75% of solution are also available for intramuscular use. If diluted with 10 ml. water, this solution may be given intravenously. As with other neuroleptic drugs, thioproperazine is indicated in states of excitement and disturbed or aggressive behaviour occurring in acute and chronic schizophrenia, mania, and delirious states. It appears to be more effective than chlorpromazine, but side-effects are much more common and severe. The drug may be given orally—or intramuscularly at first if the behaviour of the patient precludes oral administration—in amounts ranging from 20 to 60 mg. daily in divided doses. Drugs with anti-Parkinsonism actions are helpful in combating side-effects.

In chronic schizophrenia "discontinous" administration may be employed. This method is based on the view—unsubstantiated as yet—that the therapeutic effect of the drug is inseparable from the production of extrapyramidal symptoms. Increasing daily amounts of up to 90 mg. are given, pausing when considerable extrapyramidal effects appear. The effective dosage is maintained for 5 days and the drug discontinued. After 5–7 days this procedure may be repeated, and in all up to five or six courses may be given. If 90 mg. daily fails to produce extrapyramidal effects, larger amounts are given during subsequent courses at higher dosage levels; as much as 270 mg. daily may be required.

Side-effects.—The incidence of extrapyramidal disturbances is high. Parkinsonian rigidity may be intense, and the resulting akinesia may result in hypostatic pneumonia. In other patients, oculogyric crises, tonic spasms, restlessness, and respiratory disturbances such as tachypnoea or periodic breathing may occur. Sweating, salivation, and seborrhoea may be considerable, so that the resemblance to post-encephalitic Parkinsonism is close. Less commonly, disturbances of accommodation, of micturition, and of menstruation are experienced.

Barbiturates and other sedative drugs with a depressant action on the respiratory centre should not be given when extrapyramidal features are present. If sedation is required, paraldehyde and promethazine hydrochloride appear to be free from danger.

N.H.S. Basic Price.—1-mg. tabs., 100 for 15s. 4d.; 5-mg. tabs., 100 for 44s. 2d

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

The Englishman's Height

SIR,—Drs. June K. Lloyd, O. H. Wolff, and W. S. Whelen (July 15, p. 145), in their interesting follow-up of a group of obese children, conclude that "the ultimate height of the obese child, who is known to mature early, is shorter than average." But are they right? The difficulty, as I have found in connexion with another disorder in children, is to know what is average adult height. It varies with social class, district of the country, and, as the anthropometrists stress, with techniques of measurement. There is also probably a secular trend in adult height, though this is less marked than the trend to earlier maturity. R.A.F. flying personnel, Birmingham nurses, and L.C.C. children still at school after the age of 15 years are all socially and educationally selected, and so likely to be taller than average. Extrapolation, though expertly done as in Tanner and Whitehouse's standards, is less satisfactory than direct measurement.

I have not been able to find any report on an unselected group of young Englishmen who are even as tall as the present authors' sample of obese boys, in whom the average in 1959 for those older than 18 years was 68.16 in. (173.1 cm.). The most recent Army figures[1] (to which Dr. S. Rosenbaum has kindly referred me) show an average of 68 in. (172.7 cm.) for the National Service recruits of 1955 who were born in 1936 and 1937 (average age 18½ years), and an average for the whole 1955 entry, including the older, educationally and occupationally selected, deferred entry, of under 68.1 in. (173 cm.). But these Army measurements were, presumably, taken by many different observers, with some variation in technique, and the 1959 figures may show a slight increase.

I should be glad to hear of any data on the heights, carefully measured, of unselected groups of Englishmen preferably aged about 20 years.—I am, etc.,

Orpington, Kent. C. O. CARTER.

REFERENCE

[1] *Report on the Health of the Army, 1956. Section 2—Statistical Section,* 1960. The War Office, London.

Attendance at V.D. Clinics

SIR,—In your report of the meeting in Sheffield on "Promiscuity: Challenge to Religion and Medicine" (*Supplement,* July 29, p. 100), Professor R. E. Tunbridge is quoted as saying that the attendance at venereal disease clinics is very much less now than 20 years ago. If this means that fewer attendances are necessary for treatment because of improved methods, this statement is correct; but it is certainly not true of the attendance of new patients. The numbers of cases dealt with for the first time at all centres in England and Wales for the years 1938, 1939, and 1940, and in 1958, 1959, and 1960 are shown in the Annual Reports of the Chief Medical Officer of the Ministry of Health as follows: 1938, 90,678; 1939, 83,024; 1940, 72,052; 1958, 107,501; 1959, 116,462; 1960, 129,611.

The figure for 1960 is a provisional estimate based on the returns for the four quarters of the year. The

pattern of diagnoses and the methods of treatment have changed, but the number of patients who seek advice has increased considerably.—I am, etc.,

Lydia Department,
St. Thomas's Hospital,
London S.E.1. C. S. NICOL.

SIR,—You report Professor R. E. Tunbridge (*Supplement*, July 29, p. 100) as saying that "although there had been a recent increase in the attendance at venereal clinics, it was very much less than it was 20 years ago."

So far as new cases are concerned this is a widely held misapprehension. I give relevant figures for 1939 (which were more than in the years immediately following) taken from the Annual Report of the Chief Medical Officer for 1959 and for 1960, the latter culled from the four quarterly reports and therefore subject to minor revision. For 1939 and 1960, the figures for all syphilis were 11,878 and 3,867; for early syphilis 3,547 and 1,003—in 1959, 773. For gonorrhoea in 1939 and 1960 the figures were 31,300 (males 24,811 and females 6,489) and 33,640 (males 26,508 and females 7,132) respectively.

In pre-war years, most cases of non-specific urethritis (N.S.U.) were unrecognized as such, being regarded as cases of gonorrhoea. It was during and after the war that they were increasingly included amongst "other conditions." In 1960, there were 21,719 cases of separately registered N.S.U., bringing the male total of urethritis to 48,227.

For "other conditions," excluding N.S.U. from the 1960 total but with 1939 as shown in the report, the figures for 1939 and 1960 for males are 24,324 and 45,915 and for females 14,684 and 26,470 respectively. Total figures for 1939 and 1960 of all new cases are 83,024 (males 57,235 and females 25,789) and 129,611 (males 94,499, females 35,112).

Lastly, a recent survey by the Venereologists' B.M.A. Group[1] showed that "a significant proportion of Venereal Disease is treated outside the hospital service."—I am, etc.,

Hoylake, Cheshire. J. L. FLUKER.

REFERENCE

[1] *Brit. J. vener. Dis.*, 1959, **35**, 111.

Chemotherapy of Urinary and Intestinal Infections

SIR,—In the article by Drs. E. T. Knudsen, G. N. Rolinson, and Mrs. Shirley Stevens (July 22, p. 198) there is the following sentence: "250–500 mg. six- or eight-hourly is suggested for infections of the urinary tract *in view of the high concentrations of 'penbritin' obtained in the urine*." (My italics.) It is the purpose of this letter to discuss the inference in the second half of this statement—i.e., that pathogenic organisms lying free in a lumen can affect the patient.

Fourteen years ago, in this practice, we gave up using "intestinal sulphonamides." We realized that sulphaguanidine, used during the war in the dosage of 8 tablets stat. and 4 every four hours, was being used in these huge doses only because the absorbed portion (about 25%) was the active portion. We then started using ordinary systemic sulphonamides, at first sulphadiazine and later, when it became available, sulphadimidine. The latter is almost completely the reverse of sulphaguanidine in that it is 75% soluble. During the post-war period there have been many newcomers to the field of the intestinal sulphonamides, such as succinylsulphathiazole and phthalyl-suphathiazole, all evolved on the principle that the more you can produce an unabsorbed fraction in a drug the more efficient your therapy will be. We have ignored this principle. We have adhered to the principle that an intestinal infection is just as much systemic as any other, and needs a drug such as sulphadimidine in systemic doses to produce an effect, and that in sulphadimidine we have sufficient of an unabsorbed fraction to cope with organisms lying free in the lumen.

When, after the expenditure of thousands of pounds, the ideal, 100% unabsorbed, intestinal sulphonamide is discovered, we believe in established infections it will prove to be useless, although it would be satisfactory for the attack on organisms lying free in the gut for the purpose of pre-operative medication.

Now penbritin looks as if it will be effective against Gram-negative and intestinal organisms, but it should be recognized that it exerts its effect in the same way as the soluble fraction of the sulphadimidine where regularly prescribed in dysentery. There should therefore be no nonsense about giving smaller doses than in a systemic infection. Nor, because of "the high concentration of the urine," should lesser doses be given than in systemic infections. The drug is required to exert its effects long before it is concentrated in the urine, and it should be given in the same dosage as for any other infection. The teaching in the textbooks and the medical schools (with the exception of Edinburgh) is that the dose of sulphonamide can be halved in urinary-tract infections because of the high concentration of the urine. In our view, this teaching is wrong and will lead to suppression rather than elimination of the acute condition, and thus result in the all-too-frequent chronic infected state.—I am, etc.,

Great Glen, Leicestershire. G. A. STANTON.

Radioisotopes in Tumour Location

SIR,—The letter of Mr. Anthony Green and Mr. B. E. Godfrey (July 22, p. 243) requires some comment.

As they observe, an important point is the amount of isotope fixed in the tumour during the initial arterial phase. The study of isotope fixation in cerebral tumours under these circumstances is technically difficult, since it involves catheterization of the carotid system. It is therefore less generally applicable than a single injection given before operation begins. In two cases where isotope was injected intra-arterially with the counter in tumour, the tumour activity reached an almost immediate peak, then declined slightly, as, presumably, unfixed isotope left the area, but showed no increment within the next five minutes such as might be expected if the process of fixation were a slow and gradual one. The fact that, after intravenous injection, maximal activity appears in any tumour only "after several minutes" may well be due to temporal dispersion of the isotope such as does not occur when the afferent supply of the tumour is injected directly. The time interval of thirty to ninety minutes mentioned in my communication (July 8, p. 94) was not the time at which maximal activity occurred in the tumour, for this was not assessed, but merely the time during operation at which it was convenient to make the observation.

In this connexion, the uptake of ^{32}P by the cortex of a dog in the area of an inserted Geiger counter may be relevant. Maximal uptake after a single arterial injection is reached at once. There is a rapid decrement

as unfixed isotope passes from the cortical circulation, and an extremely slow elution thereafter, without phasic rises such as might occur from recirculation of the isotope. Injection of the same quantity of isotope intravenously produces a maximal activity within a minute, observation being maintained intermittently for up to one hour. The peak activity is appreciably lower than the maximal level after intra-arterial injection.

It may be, of course, that the behaviour of isotope suitable for surface counting differs from ^{32}P, which when systemically administered is readily fixed in irrelevant tissue, notably bone. An advantage of injection of the tumour's arterial supply is that all the injected isotope is offered to the tumour initially, without the abstraction of a certain proportion by these other tissues.—I am, etc.,

National Institute for Medical Research, London N.W.7. LINDSAY SYMON.

Abdominal Wound Dehiscence

SIR,—In the correspondence following your annotation on abdominal wound dehiscence (February 25, p. 568), the use of catgut in suturing the rectus sheath has been strongly condemned. Mr. Herbert Haxton (July 29, p. 308) goes so far as to say: "Does any surgeon who has thought about this problem and studied the literature really feel that he is doing the best for his patient by subjecting him to the extra hazards which the use of catgut for suturing abdominal aponeuroses entails, and, if so, why?"

In the Area Department of Obstetrics and Gynaecology at Oxford a uniform technique of suturing lower abdominal incisions has been employed for many years. Chromic catgut is used to suture the rectus sheath in every case. During the five years 1956–60 there were 2,243 laparotomies performed, 636 of which were caesarean sections and 1,607 were gynaecological operations. There were three cases of wound dehiscence in this series (an incidence of 0.13%), which compares favourably with the series quoted by Mr. H. A. Kidd (July 15, p. 173), in which 8 out of 67 wounds dehisced (11.9%). The gynaecological laparotomies include 97 Wertheim hysterectomies following radiotherapy. There was no case of dehiscence in this group, although both the effect of radiotherapy and the presence of malignant disease might be said to predispose to wound disruption.

It is suggested that the frequency of wound dehiscence is not related to the nature of the material used in suturing the rectus sheath, but rather to the care with which the upper and lower ends of the ligature are secured, to preventing strangulation of the tissues by too tight approximation, and to meticulous attention to haemostasis and asepsis.—I am, etc.,

The Radcliffe Infirmary, Oxford. A. W. G. WEIR.

Spontaneous Rupture of Colon

SIR,—I was most interested in the paper by Mr. P. L. Berger and Mr. Richard E. Shaw on "Spontaneous Rupture of the Colon" (May 20, p. 1422). I had had a similar case in May last year, and had not seen the condition described before.

My patient was a man of 60 who had always enjoyed very good health up to August, 1959, when he developed signs and symptoms of a typical rheumatoid arthritis. "Meticorten" (prednisone) 5 mg. t.d.s. afforded him excellent relief, and he had been on this dose right up to the time of his last illness. Smaller doses caused his arthritis to flare up.

I was called to see him urgently early one morning in May, 1960. His wife gave me the following history. He had been a little constipated for the last few days and had taken "agarol" as a purgative. Very early that morning he had gone to the toilet to have a motion. His wife mentioned that he remained in the lavatory about half an hour, during which time the moaning, groaning, and grunting sounded as though he was having a baby. He eventually came out stating he had been unsuccessful and asked for a dose of "epsom salts" (magnesium sulphate), which she gave him. He then took a long walk outside and returned to try again. After he had been straining and pushing for a further 30 minutes he came out complaining that he had developed a severe pain in his abdomen, which had become progressively worse, until he could stand it no longer.

On examination his abdomen was very rigid and there was generalized tenderness, especially so in the left iliac fossa and round the navel. He had not vomited. His temperature and pulse were normal, his B.P. 145/85. He was in such pain he could not lie quietly. Although he had never had symptoms indicative of a peptic ulcer, I thought he might have ruptured a duodenal ulcer which had developed as a result of his cortisone intake. I also considered the possibility of a ruptured appendix, the initial symptoms possibly being masked, again by his meticorten.

He was admitted to hospital, and before being taken to theatre for laparotomy was put on to an intravenous drip of 5% glucose with saline, to which "solu-cortef" (hydrocortisone sodium succinate) had been added. His belly was found to be full of faeces—it appeared as though someone had emptied a lavatory pail into the abdominal cavity. We were completely amazed at this discovery, and on exploring the abdomen found a tear about two inches (5 cm.) long in the sigmoid, just above the rectosigmoid junction. There were no changes in the bowel-wall to suggest diverticulitis or other disease. The abdominal cavity was cleared out, using gallons of normal saline to help wash the faeces out. The tear was sutured and a transverse colostomy established. A large drain was inserted and the abdomen closed. He was returned to the ward, where the drip was continued with solu-cortef, and a Waggenstein suction-apparatus erected. He was given broad-spectrum antibiotics intramuscularly. He survived three days. His blood pressure fluctuated from 80/? to 180/100, and at times it was necessary to give "levophed" (noradrenaline) for hours—this was added to the drip. His temperature never went above 101° F. (38.3° C.). Whether death was due to a peritonitis or due to suprarenal failure was not established. Necropsy was refused.

—I am, etc.,

Margate, Natal, South Africa. S. M. FEINBERG.

Occupational Health Services

SIR,—I would like to support whole-heartedly the excellent observations on this subject in the letter written by Mr. H. Beric Wright and Dr. Owen McGirr (July 22, p. 242). Having now as an industrial medical officer since 1946 enjoyed the same freedom of thought and action which appertained to general practice before the war, I find the fox which has lost its brush is now trying to persuade us to cut ours off.

I cannot understand either the so-called need for special training. Every industry is different and has its own special problems. Given the right type of man with a good clinical background and some general-practice experience (even under present-day conditions), the proper place for training is within his chosen

industry. Other things being equal, I would give slight preference to a man holding the D.P.H., but opportunities for special training in toxicology or other particular hazards in his own industry can easily be arranged.

The industrial medical officer is, or should be, a catalyst between management and labour. It would in my opinion be a tragedy if this state of affairs should be abolished, as it surely would be by the introduction of Government control and statutory councils. Once again it could only contribute to a destruction of the doctor–patient relationship, which makes, or did make, our profession so rewarding.

The problems of small factories could be controlled by a much-needed increase in the medical inspectorate of factories, who would advise on the necessity for the appointment of a suitable part-time general practitioner where necessary. But where an industrial medical department already exists and after many years a good human relationship exists with both management and men, why superimpose a bureaucracy which, although perhaps providing "jobs for the boys," cannot but denigrate our professional position?—I am, etc.,

Southern Region,
British Railways,
London S.E.1. L. J. HAYDON.

"Functional" Disorders

SIR,—May a general practitioner comment on the study by Drs. H. Jacobs and W. Ritchie Russell (August 5, p. 346) on their follow-up of patients seen at a neurological out-patient clinic? Their main conclusion, that they attained a high degree of accuracy in distinguishing between organic illness and non-organic illness, would appear to be fully justified by the course of events. Their plea that "out-patients should be seen by the most experienced specialists available" will be fervently echoed by all general practitioners. However, they then go on to state views on the management of patients with neurotic illness which ought not to pass unchallenged.

Firstly, their assumption that the specialist is best placed to "correct" anxiety states is quite unfounded, while their assertion that "simple and authoritative reassurance is what is chiefly needed" is contradicted in the everyday experience of general practitioners, and discloses an attitude which is astonishingly naive. They refer to the specialist's knowledge of "relevant organic disease." Relevant to what? They write of the need to study the patient's reactions to symptoms. What of the symptoms as a signal of the patient's distress? In many cases they achieve insight into their patients' plight, recognizing that "they felt themselves to be under sentence of death." But there is no appreciation that the effect of reassurance may be that the patient lives on under a suspended death sentence ("in fairly good health—still 'nervy'"—Case III) with the possibility of her later offering herself for "execution" to a cardiologist and perhaps also to a gynaecologist. No doubt *their* knowledge of "relevant organic disease" would enable these specialists to give reassurance equally authoritative, and equally futile.

Our natural desire as doctors to relieve our patients' distress promptly does not allow us to dispense with a careful examination and a proper understanding of the illness which alone can indicate the best form of treatment from those available. Drs. Jacobs and Ritchie Russell would countenance nothing less than this for a case of neurological disorder: why then should they suggest that the recognition of psychogenic illness requires merely the stock mixture of reassurance?

In respect of training, outlook, and opportunities, the specialist is the least well-placed to be of help in this situation. Curiously, the alternative mentioned by the authors, and dismissed, is the calling in of yet another specialist—the psychiatrist. Nowhere is there any hint that the general practitioner, with his unrivalled opportunities for taking a *general* view of his patient, might be capable of getting down to the task of trying to gain an understanding of the meaning of the neurotic illness. Yet there are doctors who do this: and they exist in Oxfordshire.—I am, etc.,

London N.7. J. S. NORELL.

Malaria and Glucose-6-phosphate Dehydrogenase

SIR,—In assessing the significance of falciparum malaria parasite-counts in African children with erythrocyte glucose-6-phosphate dehydrogenase deficiency and with normal erythrocyte enzymes (May 13, p. 1346) we made a comparison between subjects with parasite counts above and below 1,000 per c.mm., "since this is the level above which mortality from *P. falciparum* malaria is known to occur (Field, 1949)." Dr. T. Wilson (July 22, p. 245) alleges that we have misquoted Field,[1] stating that Field "found that case mortality rates only rose significantly when the peripheral blood before treatment showed at least 100,000 parasites per c.mm." However, the data quoted by Dr. Wilson show that of 50 fatal cases described in Field's paper 11 had parasite counts below 100,000 per c.mm., and we do not understand how he regards 22% of the total mortality as insignificant.

Field's valuable information on mortality from falciparum malaria in relation to the height of the parasite count is summarized in his Fig. 3, which is here reproduced so that readers can judge for themselves whether our quotation is correct. None of his fatal cases had parasite counts less than 1,000 per c.mm., although this was well above the threshold of parasite detection.

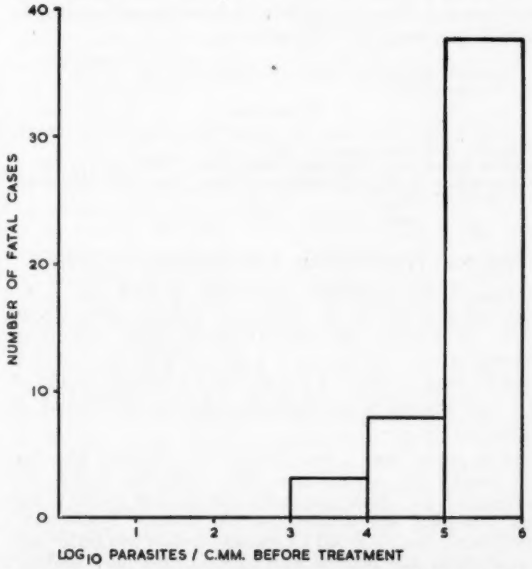


FIG.—Mortality from falciparum malaria in relation to the height of the parasite count (redrawn from Field,[1] with permission).

Dr. Wilson also complains that the parasite counts recorded in our paper were relatively low. However, we were attempting to assess whether enzyme deficiency confers protection against falciparum malaria under natural conditions—which is an important problem in population genetics. In doing so one has to take the parasite counts as they come in populations of children naturally exposed to the disease. Protection can, in fact, be demonstrated perfectly well at the parasite levels observed. In the statistical analysis of results any point of distinction between groups is arbitrary, but it is less so if there is an external reason for choosing a particular point. In this case we chose the level of 1,000 parasites per c.mm. because on available evidence, reinforced by our own experience in tropical Africa, infections with parasite counts above this level are potentially lethal, whereas infections in which the parasite counts are below this level are not. In childhood only infections which are potentially lethal are likely to be important from the point of view of natural selection. If Dr. Wilson had analysed the counts above 10,000 per c.mm., he would have found that the differences between enzyme-deficient and normal subjects are still statistically significant (χ^2, with Yates's correction for continuity, $=6.94$ for 1 d.f., $P<0.01$). Counts above 100,000 per c.mm. are rare, so that if we had considered only these we would have had too few cases for useful analysis despite the large amount of work involved in collecting and testing 876 blood specimens from young African children. However, none of our subjects with counts above 100,000 per c.mm. had enzyme deficiency, which is consistent with our hypothesis.

Points of distinction between relatively high and low parasite counts similar to ours have been applied by many other workers, including Raper,[2,3] and Vandepitte and Delaisse,[4] in assessing the protection provided by the sickle-cell trait against falciparum malaria in African children; and here the efficacy of the protection appears also in significantly reduced mortality from cerebral malaria in sickling subjects. Hence we can reaffirm with confidence that the figures published in our paper provide substantial evidence that erythrocyte enzyme deficiency in children confers protection against falciparum malaria.—We are, etc.,

National Institute for Medical Research, London N.W.7. A. C. ALLISON. D. F. CLYDE.

REFERENCES

1 Field, J. W., *Trans. roy. Soc. trop. Med. Hyg.*, 1949, **43**, 33.
2 Raper, A. B., *Brit. med. J.*, 1956, **1**, 965.
3 —— *Trans. roy. Soc. trop. Med. Hyg.*, 1959, **53**, 110.
4 Vandepitte, J. M., and Delaisse, J., *Ann. Soc. belge Méd. trop.* 1957, **37**, 703.

Apnoea, Hypertension, and Conjunctival Oedema

SIR,—I was extremely interested to read Mr. E. C. Wood's and Dr. T. A. Boliston's account (July 22, p. 217) of a case resembling pre-eclampsia occurring during a scoline apnoea. I should like to report a similar case in which I believe the signs were produced by carbon-dioxide accumulation during the period of apnoea.

The patient was a primigravida of 37 years who had a history of hypertension—B.P. 185/110—during her pregnancy, for which an attempt was made to induce labour by rupturing her membranes and giving "syntocinon" (oxytocin). As this failed a caesarean section was performed. Anaesthesia was induced with cyclopropane and "scoline" (suxamethonium chloride), followed by intubation and controlled respiration with nitrous oxide and oxygen using a circle absorber. The baby was delivered and cried at once, the operation being completed within 45 minutes, during which time the patient made no attempts at spontaneous respiration. A short period (2–3 minutes) of 95% oxygen and 5% carbon dioxide was tried, but as no signs of spontaneous respiration appeared this was stopped and controlled respiration was continued with 100% oxygen for an hour, when spontaneous but inadequate respiration reappeared which was assisted manually, using a 50:50 nitrous-oxide–oxygen mixture. Her pre-operative blood-pressure was 185/110 and during the operation there had been little variation.

After 10–15 minutes of assisted respiration muscular twitching was noted involving her arms, legs, and abdomen, resembling that which precedes an eclamptic convulsion or a convulsion modified by relaxants. Her colour was good, but she was sweating and the blood-pressure had risen to 230/140. The soda lime in the absorber was changed and the patient was hyperventilated. The twitching stopped after 5–10 minutes and her blood-pressure fell to below the pre-operative level. "Apresoline" (hydrallazine), 20 mg., was given intravenously. After a further hour of fully controlled respiration adequate spontaneous respiration returned and her general condition and blood-pressure remained satisfactory.

Whilst the patient was hypertensive before the operation, she never showed either oedema or albuminuria. That, and the rapid disappearance of twitching, etc., with hyperventilation, makes it unlikely to have been an eclamptic fit modified by relaxants, but rather the effects of carbon-dioxide build-up during a period of inadequately assisted respiration with a high percentage of oxygen. The apnoea was undoubtedly due to interaction of suxamethonium and oxytocin which was used in the attempted induction of labour. The subsequent progress of mother and baby has been very satisfactory.—I am, etc.,

The Royal Infirmary, Hull. J. L. WEBSTER.

Suicide with Thioridazine

SIR,—Thioridazine is a relatively new phenothiazine tranquillizer, marketed as "melleril" by Sandoz Ltd. It is claimed to be singularly free from the side-effects associated with the use of the other phenothiazines, and, in view of its reputation for safety, large amounts are dispensed at a time. This case demonstrates that amounts properly in a patient's possession may be used to commit suicide.

D. G., a spinster aged 47 who had been treated for ten years as a schizophrenic. For the previous year she had been receiving thioridazine 300 mg. daily. In her terminal episode she first complained of giddiness and then started to vomit. She became comatose and cyanosed and breathed stertorously. She did not respond to painful stimuli. Her pupils were partly dilated and responded irregularly to light. There was a left extensor plantar response, and that on the right was equivocal. The lower limb reflexes were feeble; those in the upper limbs were exaggerated on the right and diminished on the left. Some fine rales were heard in the lungs. The pulse remained regular at 68 beats per minute. A diagnosis of cerebrovascular accident was made, and she was given 15 mg. of morphine. She continued to deteriorate, and died 12 hours later. A note was found.

Necropsy showed a well-nourished adult woman. The only natural internal disease was early bronchopneumonia throughout both lower lobes. There was oedema of the right arytenoid fold, thrombosis of the posterior laryngeal plexus, and intense congestion with focal haemorrhages of an area about 7 by 7 cm. on the greater curve of the stomach where a bolus of white powder lay. The liver showed extreme toxic change with yellowish areas of incipient

necrosis. The stomach contained 150 ml. of slightly blood-stained fluid and some whitish powder. The powder (dry weight 10.4 g.) consisted mostly of starch morphologically identical with that in melleril tablets, and scrapings from the cut surface of one of these and the powder found in the stomach contents both contained approximately 2% of birefringent granules. Extraction of both with normal hydrochloric acid gave a clear, pale blue solution, and when treated with nitrous acid, iodic acid, and ferric chloride (reagents C, D, and E of Cooper[1]) both extracts gave yellow, orange, and green colours respectively. No other likely drugs were detected in blood or urine. Urinary analysis[2] indicated a dose in excess of the maximum therapeutic amount, and urine diluted 1 in 10 indicated ingestion of about 8 g. The amount of thioridazine corresponding to the starch vehicle in her stomach is approximately 2 g. These estimates are not close, but it is clear that she had taken a lot more than her normal daily dose, perhaps about 5 g.

The urinary deposit contained a small number of red cells and some granular casts. A moderate amount of protein but no glucose was present, and the *p*H was 6.7. The kidneys were histologically normal, but the liver showed some intercellular oedema and pigment-retention in the cell chords. There was some perivenous degeneration and a little fatty change. The alkaline phosphatase, thymol turbidity, and zinc sulphate flocculation tests were all within normal limits for cadaver sera,[3] but the bilirubin was 1.3 mg., of which 1 mg. was direct reacting.

In the only comparable case found, levomepromazine was taken in a dose of 250 mg. five hours after 1,000 mg. of thioridazine with suicidal intent.[4] In this case, also, deep coma developed with absent tendon, skin, and corneal reflexes, and death occurred on the fifth day, apparently from severe toxic nephropathy.

Two points emerge. Firstly, thioridazine in excessive dosage may have a neuroplegic action and mimic the signs and symptoms of cerebral catastrophe. Secondly, it can be used for taking life. In this case death was apparently due to direct action on the brain, neither kidneys nor liver being markedly affected in the short time elapsing between ingestion and death.

This case is published by permission of H.M. Coroner for Metropolitan Essex.

—We are, etc.,

East Ham Memorial Hospital, London E.7. J. B. ENTICKNAP.
Goodmayes Hospital, Ilford, Essex. B. GORDON.

REFERENCES

[1] Cooper, P., *Pharm. J.*, 1954, **173**, 481.
[2] Forrest, I. S., Forrest, F. M., and Mason, A. S., *Amer. J. Psychiat.*, 1960, **116**, 928.
[3] Enticknap, J. B., *J. forensic Med.*, 1960, **7**, 135.
[4] Guerin, A., *J. Méd. Bordeaux*, 1960, **137**, 748.

Intraperitoneal Haemorrhage from Fibroids

SIR,—The communication by Mr. Abdel Hamid Badawy (March 11, p. 717) and the letter from Dr. D. J. Cannon (June 3, p. 1605) prompt me to write of a more recent case in my experience.

A nulliparous married woman aged 44 years complained of fairly sudden onset of generalized abdominal pain on the morning of July 1, 1961, and later in the day experienced right shoulder pain. On examination her temperature was 98.8° F. (36.9° C.). She did not appear pale or shocked. Her abdomen showed generalized tenderness, and a mass was felt in the left lower quadrant. In view of a fairly long-standing history of recurrent episodes of mental derangement and the fact that my assistance had not long ago been sought in connexion with certification for admission to a mental hospital, I was asked especially not to examine her prior to induction of anaesthesia.

Under anaesthesia at 5.30 p.m. on July 1 I found her uterus a mass of fibroids, and, in view of the history and her doctor's findings, considered that one of the fibroids had probably undergone red degeneration. On exploring the abdomen, the peritoneal cavity was found to contain two pints (1.1 litres) of fresh blood which was seen to be coming from a ruptured vein on the surface of a pedunculated fundal fibroid, 3 in. (7.6 cm.) in diameter. There were also three other intramural fibroids of similar size and several smaller ones.

Ordinarily I would have performed a total hysterectomy, but the patient's own doctor, who has attended her often in the past, considered that the desire for a child was still important to her and that to deprive her of all hope in this respect might well have a bad effect on her mental state. Therefore I removed only the fibroids. Recovery was uneventful both physically and mentally.—I am, etc.,

Guernsey, Channel Islands. C. H. J. REY.

Fusion of Labia Minora

SIR,—I was interested in the description by Dr. C. J. Carr (July 29, p. 314) of his patient with fusion of the labia minora. I saw a similar patient some years ago.

The patient was a maiden lady aged 76 who complained that she had passed urine only in dribbles for 20 years, and that she was never dry. Examination showed apparently complete fusion of the labia minora. She would not attempt to pass urine in my presence, but when she had done so in the lavatory there was considerable distension of the pouch formed by the fusion of the labia minora, with a drop of urine issuing through a pin-hole opening at the uppermost limit of the line of fusion. This orifice was enlarged very slightly by probes, and several hours later, under local anaesthesia, the labia minora were separated with difficulty through dense fibrous tissue. The functional result was excellent and she had no further urinary troubles up to her death at age 86.

The relevant past history was that in her mid-fifties she had a perianal abscess with extensive surrounding inflammation spreading forwards to the vulva. This she tolerated for weeks before seeking surgical relief. —I am, etc.,

Leeds 7. G. W. LEWIS.

SIR,—Dr. C. J. Carr's letter (July 29, p. 314) on fusion of the labia minora reminds me of a Sudanese girl whom we attended in April, 1960.

As a child she had a ritual circumcision. She was married and was expecting her first baby. In the perineal area there were two openings rather similar in appearance. One was the anus, the other the urogenital opening. The surrounding area was freely mobile even over the symphysis.

The first stage of labour was normal. In the second stage, under a general anaesthetic, the posterior shelf was divided to reveal a normal vaginal opening and an anterior shelf to reveal the urethra. After a forceps delivery, the labia minora were refashioned to prevent a renewal of adhesions across the midline. Without help this patient would have been severely torn, and subsequent adhesion and scarring would have resulted in the condition which Dr. Carr has described.—We are, etc.,

C. H. DE BOER.
Liverpool. I. GOTTLIEB.

Psychopaths Aged over 25

SIR,—With reference to Dr. Seymour Spencer's letter (August 5, p. 379), I feel it would be useful for the subsequent events relating to this case to be stated.

On the recommendation of the Review Tribunal who had ordered that the category of the detention order should be altered from "mental illness" to "psychopathic disorder," this was accordingly done. Subsequently, the question as to whether the patient was still liable to be detained since she was now classified as a psychopath was raised with the clerk of the Review Tribunal, who referred the matter to the legal advisers of the Ministry of Health, who, after some days, ruled that the patient was not now liable to be detained. The patient agreed to remain informally, but left after 10 days.

Consequently, until further consideration has been given to the position arising in this case it would appear that psychopaths aged over 25 years cannot be detained in these circumstances, and it would appear that the appropriate way of dealing with such cases would be under section 60 of the Mental Health Act, 1959, by a court order, which section 63 (3) (b) makes possible.—I am, etc.,

Tone Vale Hospital,
Near Taunton. K. C. BAILEY.

Staphylococcal Infections

SIR,—I read with great interest the papers on staphylococcal infections (August 5, pp. 329–339). Staphylococcal infections, like boils and abscesses, are common complaints in general practice and they are usually treated by general practitioners. I was puzzled for some time by so many cases of boils in practice and I decided to investigate them closely.

I have found out[1] that the majority of patients suffering from boils were the patients suffering from allergic diseases. This observation fits into the accepted theory that nasal carriers of *Staphylococcus pyogenes* suffer from staphylococcal infections. Hay-fever or allergic rhinitis predisposes the patients to sinusitis and to staphylococcal infections of anterior nares. It is known that patches of eczema are infected with *Staphylococcus pyogenes*. Research on staphylococcal infections should include both the staphylococcus and the patient. It is unfortunate that, of these two, the patient is often forgotten.—I am, etc.,

Allergy Clinic,
North Lonsdale Hospital,
Barrow-in-Furness, Lancs. B. BENDKOWSKI.

REFERENCE

[1] Bendkowski, B., *Acta allerg. (Kbh.)*, 1961, **16**, 81.

Panic Immunization

SIR,—Dr. E. J. Moynahan's letter (July 15, p. 173) to me seemed a reasoned criticism to the suggestions in the article by Dr. Guy Bousfield (July 1, p. 43). Dr. Bousfield now writes a long letter (July 29, p. 312) which I had hoped would be a reasoned reply. Instead, "I am not even prepared to discuss the matter with him."

I am sure we do want this matter discussed. He implies that pertussis vaccine alone or combined with other antigens is sometimes responsible for "giving them [allergic children] objectional complaints such as asthma, eczema. . . ." What evidence is there that this occurs more often in allergic (*sic*) than non-allergic man? I and, I am sure, Dr. Moynahan would be grateful for this evidence.—I am, etc.,

A. W. FRANKLAND.

Allergy Department,
The Wright-Fleming Institute of Microbiology,
St. Mary's Hospital, London W.2.

Plague Documents

SIR,—Dr. Paul Cassar's article (August 5, p. 377) describing the wooden "documents" still in existence in Malta, which were used because of the fear of infection possibly carried by paper, makes fascinating reading. He cites this as a reminder of the fallacies of epidemiological thought only 150 years ago. But this fear was still prevalent less than 70 years ago.

My father, the late Dr. Frank Radcliffe, was a ship surgeon on one of Alfred Holt's Blue Funnel line trading to the East Indies in the early 1890's, and used to relate with relish how his duties required him to take the ship's papers ashore at Algiers for inspection before anybody was allowed to land. He was rowed to the foot of the harbour steps to the medical officer's office, which had no direct access to the quayside. The papers were then handed through an inspection window, and opened out with two pairs of metal forceps which had previously been disinfected by flaming, so that they were not touched by hand. Only after this ritual was he allowed to be rowed round to the main landing steps leading to the office and received inside by the port medical officer.—I am, etc.,

Wivenhoe, Essex. WALTER RADCLIFFE.

Latent Brucellosis in Farmers

SIR,—May we reply to the letter of Dr. Frederick J. Wright (August 5, p. 382) criticizing our use of the term "latent brucellosis"?

We did not define the term because we considered that such definition was implicit in the third paragraph of our article (July 8, p. 80). "Latent" means to us no more and no less than the clumsier term "subclinical." Our subjects were considered to have latent infections because there was no clinical evidence of present illness. Whether the infection is past or present seems to us of small importance in such an epidemiological study. What matters is that a certain number of farmers showed evidence of having at some time acquired the infection. In any case, who can say when the last organism has been eradicated?—We are, etc.,

I. R. MCWHINNEY.
Warwick. A. P. PRIOR.

Sobering-up

SIR,—There is one method of rapid "sobering-up" (May 6, p. 1306) which I imagine many house officers have used on casualty duty, but anyone who has not heard of it may on occasions find it useful. As the effect is very transient it is of limited application. I have used it only two or three times, for the same type of case each time, and it has always worked. It is very useful where the patient is found comatose or nearly so, unrousable but smelling of alcohol, and it is important to find out either who he is, or whether he has been involved in an accident and at least partly concussed.

Two ml. of nikethamide is injected intravenously. The patient sits up and sneezes once or twice and asks where

he is. For five or ten minutes he remains sober enough to give an account of himself, and then goes back to his snoring.—I am, etc.,

Singapore. BRUCE H. BOEREE.

Light After Dark

SIR,—I have just received the July 15 issue of the *Journal*, and was amused to read the letter from Dr. David A. Herd (p. 179) entitled "Light After Dark."

Perhaps the attachments are not yet available in England, but I have a perfectly good "trouble" light (North American for inspection lamp), with a plug which fits into the cigar-lighter of my car. I also have a small electric bottle-warmer with the same fitting, with which we are able to warm the baby's feeds on a journey. Perhaps, therefore, it is the makers of accessories, rather than the makers of cars, who have no imagination.—I am, etc.,

The Victoria General Hospital, Halifax, Nova Scotia. J. F. FILBEE.

Lolly Rash?

SIR,—During the past few weeks I have encountered an unusual type of rash in children, all of whom were otherwise quite well. On close questioning it seems that the only factor common to all the cases is that each child had eaten iced lollies not long before the rash appeared. Treatment with antihistamines has been successful.

I would be interested to know if any other practitioner has noticed any similar association.—I am, etc.,

Plymouth. ALUN LLOYD-JAMES.

POINTS FROM LETTERS

Childhood Obesity

Mrs. P. RODWELL (Ipswich) writes: I wonder if doctors who are so concerned with obesity in children realize the incalculable harm they are doing to children's minds. Children are creatures with hearts, souls, feelings—and their feelings are already exacerbated by the knowledge that fat is not conducive to beauty of form. Fat children are, these days, criticized by their schoolteachers, frowned upon by their doctors, teased by their fellows, and horrified by their mirrors—and reduced to such a state of anxiety that their sleep is disturbed and their waking hours made hideous by the knowledge that each day brings only—more criticism, more teasing. . . . As the mother of two children who are now, thank goodness, growing out of an obese stage, I would appeal to doctors to give some thought to the harm which may be done to children through this modern emphasis on obesity, and I would beg them to direct our children's teachers to leave the physical state and problems of the young where they belong—in the hands of doctors only.

Fusion of Labia Minora

Dr. R. H. LINDENBAUM (London, N.W.3) writes: I hesitate to intrude merely bookish learning, when Dr. C. J. Carr (July 29, p. 314) is on the spot in Mbale. But, despite the woman's statement, could this peculiar case be the result of infibulation, or artificial closure of the vagina?

Poison on the Land

Dr. SUZANNE ALEXANDER (Oxford) writes: It has been pointed out to me that I confused (July 29, p. 310) hexachlorobenzene and benzene hexachloride. It is hexachlorobenzene, used as a fungicide for wheat in Turkey, which causes porphyria. Benzene hexachloride is a different substance.

Obituary

C. V. PATRICK, M.B., Ch.B., F.R.C.S.

The obituary of Mr. C. V. Patrick was published in the *Journal* of July 15 (p. 181).

W. R. S. H. writes: The death of Conrad Vincent Patrick has removed one of the most prominent figures in the surgical life of the West Midlands. The son of a Leicester doctor, he was educated at Rugby and Caius College, Cambridge. At St. Thomas's Hospital he had a brilliant career, winning the Chesenden, Solly, and Clutton medals. Though of well-to-do parents, he was justly proud of the fact that his medical education had cost them nothing. After holding the usual junior appointments, he became resident assistant surgeon at St. Thomas's. This was one of the most coveted surgical posts in London, short of a staff appointment, and to the select few who achieved it a wide choice of career lay open. After much thought Patrick decided to renounce the academic life, and, resisting an appeal by the late Sir Percy Sargent to stay on in London and practise neurosurgery, he went to seek his fortune in Wolverhampton. Here, in 1930, he was elected to the honorary staff of the Royal Hospital.

Fortune he soon found in a private practice so large that this alone would have taxed the physical strength of most men. But it was at the Royal Hospital that his real life work lay. Here he became associated with a group of brilliant colleagues which included J. H. Sheldon, S. W. Maslen-Jones, S. C. Dyke, and R. Milnes Walker. In this remarkable team Patrick played a prominent part in raising the standards and reputation of the hospital to a level which put Wolverhampton in the forefront of the non-teaching provincial centres. To the fulfilment of this task he brought a mind acute and powerful, a limitless capacity for hard work, and an indomitable will. The improvement of the hospital was always uppermost in his mind, and he kept a vigilant and far-seeing eye upon every threat to its welfare. As with other men of outstanding ability, the demands upon his time and services were immense. His cool wise head, common sense, and diligent attention to business made him an ideal committee man, and he was always the obvious choice for service of this kind.

"C. V. P." was a true general surgeon, prepared, in his younger days at least, to tackle anything, but it was in the surgery of cleft lip and palate and of hypospadias that Patrick showed his real quality. During the last fifteen years of his life he specialized in urological surgery, and this work formed an ever-increasing proportion of his lists. As an operator, he belonged to the "true faith." Unusual skill and dexterity enabled him to complete a long and heavy list yet still have time for consultations, or to take the chair of the regional advisory committee in surgery at Birmingham. But he was no speed merchant; all his work was characterized by scrupulous care, and he never "cut a corner" for the sake of a few minutes spared. Last, but perhaps not least, he had style—that indefinable quality which alone gives pleasure to the spectator.

At the bedside his shrewd clinical sense and judgment were supported by an astonishingly wide knowledge of recent progress in surgery. He was an excellent teacher, and as reader in surgery at Birmingham University he conducted a weekly teaching round which was always crowded.

His encyclopaedic knowledge was the result of wide reading to which hours were devoted every evening—every evening, that is, unless there was a party, for C. V. P. loved a party, and there were plenty of them at No. 55 Waterloo Road. Mrs. Patrick's dinners were famous, and he was at his very best as a host.

He had many hobbies. Soon after the second world war some concern was caused among neighbours by the appearance of what seemed to be a large anti-aircraft gun on the lawn of his garden. These fears proved groundless. C. V. P. had become an astronomer and the gun was his latest telescope. He loved his garden and took particular interest in the orchard, which he always tended himself. It was here that he kept the bees which gave him endless pleasure. He was a real expert with bees, and his advice was widely sought.

But perhaps his greatest pleasure came from friendship with old house-surgeons and registrars, with whom he always kept in touch and in whose careers he took the greatest interest. For all of these during their time in Wolverhampton, for his junior colleagues, and indeed for all who worked with him, C. V. P. proved a mighty champion, fighting and winning, with monotonous regularity, all their battles for them. In characteristic style, CVP 55 was stamped upon the number-plate of his car, but Osler's "master word in medicine" was stamped upon the driver's heart, and he filled the unforgiving minute with sixty seconds' worth of distance run.

J. M. MITCHELL, *M.C.*, M.B., Ch.B.

Dr. J. M. Mitchell, who practised in West Bromwich for 42 years, died in Hallam Hospital on August 3. He was 68 years of age, and was actively engaged in practice until the date of his collapse three weeks previously.

James Mitchell Mitchell was born at Stonehaven, Aberdeenshire, and graduated M.B., Ch.B. at Aberdeen University in 1915. In the first world war he joined the Lincolnshire Yeomanry, and while in charge of a field ambulance unit in Palestine he was awarded the Military Cross and mentioned in dispatches. Soon after returning in 1919 he went into partnership with his former colonel, the late Dr. A. C. Goodwin, in general practice in West Bromwich, where he remained for the rest of his life.

Dr. Mitchell's numerous activities in the interests of his profession left him all too little time for leisure. He was a former chairman of the West Bromwich and Smethwick Division of the British Medical Association, and also served as its secretary for over 30 years. During his term of office he represented his Division on several occasions at the B.M.A. Annual Meetings. The Division is indeed deeply indebted to Dr. Mitchell, for when he took office it was almost defunct, yet, largely owing to his great interest and enthusiastic efforts, it eventually developed into the flourishing and active organization it has remained ever since. He was also a member of the local medical committee for a corresponding period. For several years he acted as anaesthetist to West Bromwich Workhouse Infirmary, and took part in its conversion into a large municipal general hospital (the present Hallam Hospital), subsequently accepting the post of medical officer to Wigmore Schools, West Bromwich, a position which he held until they were eventually closed. Throughout the second world war he was chairman of the Services medical board at Smethwick.

In 1948 he was appointed to the West Bromwich Executive Council and later served as its vice-chairman. He also sat on the West Bromwich education and health committees and was doctor to the West Bromwich Albion Football Club for more than 20 years. He believed implicitly in fostering closer contacts between his fellow practitioners, and assisted in founding a local medical practitioners' luncheon club, of which he remained chairman up to the date of his death.

Dr. Mitchell was the longest-serving doctor in West Bromwich, and, despite the increased demands imposed by the advent of the Health Service, he never failed to fulfil the dual role of family doctor and friend. His outstanding success in general practice was based originally upon his wide obstetrical experience and ability. His views always commanded respect, and his sympathy and understanding not only caused him to be greatly loved by his patients but also gained him a wide circle of friends. Of no man could it be more truthfully said that the whole of his life was spent in unremitting and ungrudging service. It is much to be regretted that his untimely death prevented his contemplated and well-deserved retirement.

His principal hobbies were reading, contract bridge, and golf—he was one of the oldest members of the Sandwell Park Golf Club. He was a distinguished Freemason, having been Worshipful Master of his Lodge and having attained Provincial honours. He had a wonderful sense of humour, which not only lightened his burdens but also greatly endeared him to his innumerable friends and colleagues. He will be sorely missed, and the sympathy of all who knew him will be extended to his wife and two sons.—J. H. H.

D. S. writes: Jim Mitchell's impact, albeit over 28 years ago, on a raw young practitioner should not at this time go unremarked. When one first settled in West Bromwich, recently qualified but in single-handed practice, it was Mitchell who promptly took one under his wing. He brought to life the Hippocratic Oath not merely in his dealings with his patients but in his readiness "without fee or covenant . . . to impart his art by precept, by lecture, and by every mode of teaching" to a stranger, who, having embraced the "Law of Medicine," was accepted by him as a brother. His help extended from the giving of wise advice to turning out in the small hours, with no question of material recompense, to lend his great obstetric skill to the anxious greenhorn. One's own happy life as a family doctor and an active member of a medical community owes more than can be reckoned to his teaching, and to the inspiration of his example of service to the people among whom he lived and to the profession which he loved. Professionally he was father and brother to a younger colleague who cannot let pass the end of a 28-year friendship and the loss of a kindly understanding family doctor without offering his inadequate tribute.

BARBARA M. MACEWEN, O.B.E., M.D.
M.R.C.O.G., D.P.H.

Mrs. Barbara M. Macewen (née Cunningham), formerly a medical officer of the Ministry of Health, died in Scotland on August 8, aged 83.

Barbara Martin Macewen was born on August 26, 1877, and graduated M.B., Ch.B. at the University of Edinburgh in 1901, obtaining the L.M. at the Rotunda in the following year. After some years in India at one of the Lady Ava and Dufferin hospitals, she took her Edinburgh doctorate in 1909 and the Cambridge D.P.H. in 1910, next serving as assistant medical officer of health and inspector of midwives in Manchester until she became a medical officer with the National Insurance Commission. She was appointed O.B.E. in 1918. In 1920 she transferred to the Ministry of Health. She resigned in 1925 on her marriage to the late Dr. Hugh Macewen, a senior medical officer of the Ministry of Health, but returned to the Ministry to assist in the big inquiry into maternal mortality of the early 'thirties, and obtained her M.R.C.O.G. in 1937. She again returned at the outbreak of war, but retired with her husband from the Ministry in 1941. After two years at Ulverston, where her husband was acting medical officer of health, they went to Ballochmyle Hospital in Ayrshire, of which he was the temporary medical superintendent until his final retirement to Innellan on the Clyde. After her husband's death in 1955 she lived in Edinburgh.

N. M. G. writes: Barbara Macewen was of Border stock, her father having been factor of the Duke of Buccleuch's

estates. She was passionately devoted to her work, and her caustic comments on those she suspected of less single-minded devotion to detail earned the hostility of some, but her warm heart and championship of those she liked made her the friend of many more. A great lady and a great character, she was the representative of her age—and perhaps the mould has been broken.

A. M. FRASER, M.D., F.R.C.P.Ed., D.P.H.

Dr. A. M. Fraser, senior administrative medical officer to the Northern Regional Hospital Board of Scotland, and formerly medical officer of health of the burgh and county of Inverness, died in hospital at Inverness on July 27. He was 60 years of age.

Alexander Mackenzie Fraser was born at Kingussie, Inverness-shire, on May 19, 1901, and was educated at Kingussie secondary school and Aberdeen University. He graduated M.B., Ch.B. in 1924 and proceeded M.D. in 1929, taking the D.P.H. in the same year. After graduation he was a resident medical officer in the Royal Northern Infirmary, Inverness, the Royal Hospital for Sick Children, Aberdeen, and the Aberdeen City Fever Hospital. In 1929 he was appointed medical officer of health for the burgh and county of Inverness, and at the beginning of the National Health Service secretary and senior administrative medical officer to the Northern Regional Hospital Board. Elected F.R.C.P.Ed. in 1957, he was Honorary Physician to the King from 1947 to 1950.

E. A. J. writes: I first met Sandy Fraser many years ago when we were residents in the Aberdeen City Hospital together, and I have worked in close association with him for most of the years since then. Sandy gave great promise of things to come in those days, and the promise was duly fulfilled. Even then he was intensely interested in medical administration. He was a sound clinician, but he was always more interested in the provision of medical services than in clinical work.

He came to Inverness in 1929 as temporary medical officer of health on the recommendation of the late Dr. J. Parlane Kinloch, chief medical officer to the Department of Health for Scotland, and he so impressed the local authority that within six months they appointed him to be their medical officer of health. I am sure that they never regretted this step.

Not only Inverness but the whole of the North of Scotland has much for which to thank him. It was he who made bacteriological services available to the general practitioners in the area. He was largely responsible for the provision of consultant physicians—there being none before he came—and also of obstetricians. These are only a few of the services he sponsored. Further afield he was instrumental in starting the School for Spastics in Edinburgh, and he was honorary secretary of the Scottish Council for the Care of Spastics. I am sure that there was no better-known medical man throughout the length and breadth of Scotland. He was recognized by all his medical colleagues as a great administrator and a man possessed of vision which few could equal. He was teeming with personality and enjoyed life to the full.

By his passing the Highlands have lost not only the man who has done more for the medical services in the region than anyone else but a personality whose opinion was respected throughout the country. We will miss him sadly, and Inverness will not be the same place without him.

J. J. KEMPTON, M.B.E., M.D., F.R.C.P.

The obituary of Dr. J. J. Kempton was published in the *Journal* of August 5 (p. 388).

H. L. M. writes: I cannot let the death of my dear friend and colleague pass without a tribute. He showed a complete and rounded personality from whatever aspect it was regarded. The intellectual power was acknowledged: every article he wrote clearly expressed something of originality. His remarks at meetings were equally to the point and always delivered without notes and with never a falter. Most men placed in charge of a department at an early age start rapid empire building: not so Jack Kempton. His first action was to reorganize, so that greater efficiency was obtained with half the number of beds. Then enthusiasm tempered by foresight gradually built up a department, thought by his colleagues to be second to none. The warm affection and respect in which he was regarded by his surgical as well as his medical colleagues was shown by the fact that children admitted for surgical treatment were also placed under his care by the surgeons, with, as a result, a speeding of their recovery and a shortening of the surgical waiting-list.

Jack Kempton delighted in human company and social activities. At the paediatric meetings at Windermere he organized sailing races on the lake. Few physicians sail their yachts to medical conferences, but this he did to Amsterdam and Copenhagen. Last year's annual leave was spent sailing a yacht to Bermuda and flying to New York to spend a week in the children's hospitals before a flight home. Many an off-shore sailing race and cruise have I spent in his company when other qualities became apparent—in particular, his extremely good temper under stress, imperturbable courage, and great physical endurance. I well remember arriving off Margate after five days' beating against wind and sea from Kiel. Everyone was exhausted, except Kempton. There was an hour to wait for the tide, so we anchored and all immediately fell into a deep sleep, all that is except Kempton: he remained on watch to wake us (with a cup of cocoa) in an hour's time.

The sense of loss that pervades all who knew him cannot be expressed in words by me, but perhaps something of our feelings towards Jack Kempton and some hint of the varied facets of his outstanding personality may be inferred from the few notes here written with deep affection.

Medico-Legal

MENTAL TREATMENT UNDER CONSTRAINT

[FROM OUR LEGAL CORRESPONDENT]

On May 24 the chairman of the Middlesex Sessions Appeals Committee remanded an 18-year-old prisoner who had a record of offences against children in order that a hospital could be found which would accept him for treatment (*The Times*, May 25). Medical witnesses stated that the man was in need of medical treatment and should not go to prison or borstal, but the Home Office and the Ministry of Health had been unsuccessful in getting a hospital to accept him. On the adjourned hearing on June 21, the court was told that a hospital had agreed to accept the prisoner but that it was an open hospital which the prisoner had been to before and from which he had walked out. To avoid a further remand, the court made an order under sections 60 and 65 of the Mental Health Act, there and then ordering his detention in the hospital which had agreed to accept him.

Detention for Forty Years

On June 29, at Bristol Assizes, Ronald Derek Sowle, aged 30, a former mental patient, was found not guilty of murder but by reason of diminished responsibility guilty of manslaughter of Diana Marion Locke, a 17-year-old schoolgirl (*The Times*, June 30). Sowle, formerly compulsorily detained in hospital, was reclassified three days before the girl died. Sowle discharged himself from the psychiatric hostel the evening after the girl's death.

Mr. Justice Stevenson made an order under section 60 of the Mental Health Act for Sowle's detention at Rampton, and made a further order under section 65 restricting his discharge for 40 years. The judge added that he hoped a most searching inquiry would be made into the circumstances in which Sowle came to be reclassified.

Medical Notes in Parliament

ADMINISTRATION OF INDUSTRIAL INJURIES ACT

COMPREHENSIVE OCCUPATIONAL HEALTH SERVICE NEEDED

[FROM OUR PARLIAMENTARY CORRESPONDENT]

A review of the administration of the Industrial Injuries Act in which the Commons engaged on August 1 brought again to notice the absence of an industrial health service and the very small amount provided from the Fund to finance research, as illustrated in the figures given to Lord Taylor in the other House a few days earlier.

Lord BALNIEL (Hertford), from the Conservative side, voiced the disappointment of many members interested in the Health Service that the preventive side of the Service had not developed as they would have liked, and said bluntly, "It is no more than a pipe dream to imagine that an industrial health service will be established on the Health Service Estimates in anything like the next four or five years." The immense claims of hospital building, mental hostels, and higher pay for doctors and auxiliaries all had a higher priority. But the fact that it could not be borne on the Estimates did not in any way lessen the need or urgency for it.

B.M.A. Quoted in Support

Lord Balniel recalled the recommendation of the Dale Committee in 1951 for eventual comprehensive provision for occupational health, and emphasized this with a quotation from the recent B.M.A. report on *The Future of Occupational Health Services* that ". . . the British Medical Association urges that an immediate beginning be made in setting up a comprehensive occupational health service." He linked this lack with that on research, about which others had spoken, by suggesting that from the £70m. surplus in the Industrial Injuries Fund the Minister should consider the possibility of devoting a slightly larger sum to finance research, in anticipation of the time when an industrial health service could be established.

Mr. H. R. GOWER (Barry, Con.) went much further in asking for a "dramatic" increase for what was a specialized form of research which would probably bring a long-term benefit to the Fund itself. Mr. D. JONES (Burnley, Lab.) reinforced his plea for extended research by quoting textually the questions of Lord Taylor and the answers he received.

Research for a "Proper Purpose" Admissible

Mr. J. BOYD-CARPENTER, Minister of Pensions and National Insurance, of course had to point out that fundamental research was not the business of his department. It was only research related to the prescription of industrial disease, under powers contained in section 73 of the Act, that brought him into the picture. If any scheme really coming within the section was put to him where research would serve a proper purpose, he would be very willing to consider it. But he could not set up a rival medical research installation in competition with the Ministries of Science, Health, and Labour.

Pneumoconiosis Boards

Mr. H. FINCH (Bedwellty, Lab.), opening the debate with an examination of the statistics of industrial disability and some anomalies in benefits and compensation, raised a point about men examined by pneumoconiosis medical panels and radiological category I, having been found not to have pneumoconiosis but to have some dust on the lung. He asked that in these circumstances men should be informed even when there was only a small dust retention on the lung, instead of being allowed to leave the board under the impression that there was no lung disability whatever. Mr. BOYD-CARPENTER said on this that he had been considering whether there would be any practical difficulty in sending the man a brief note saying, "You are found to be free of pneumoconiosis." But the problem arose, perhaps in one case in 100, where the *x*-ray revealed not pneumoconiosis but something more sinister. It would be very wrong to write to a man "out of the blue" and tell him he had cancer of the lung. On the other hand, to make a practice of sending a letter which said, "You are free of pneumoconiosis," which would be literally true, would be open to justifiable criticism if a more serious complaint were ignored. It was a difficult problem which he was anxious to deal with, and he thought it might be possible to evolve a formula which related specifically to pneumoconiosis and did not purport to give a medical opinion on the man's lungs from other points of view.

Disability from Bronchitis

The other subject to which much attention was given was the assessment of disability from bronchitis and emphysema in relation to pneumoconiosis. In these circumstances, Mr. FINCH argued, the board should declare that a man was suffering from pneumoconiosis, as was done in Australia. It was impossible to dissociate them during lifetime, and in many cases on death it was impossible to assess the degree of the three diseases separately. He asked also for a right of appeal on diagnosis issues.

Mr. R. SHARPLES, the Parliamentary Secretary, making his first speech in that capacity, rested on the argument that the Industrial Injuries Advisory Council in 1953 had declined to change the statutory definition in section 53 (3) of the 1946 Act, or to widen the regulations. One difficulty was that bronchitis and emphysema were common among the population as a whole. In Australia, as in South Africa, bronchitis was not a common disease. This did not satisfy M.P.s from mining and other industrial areas, whose arguments were summed up when Dr. BARNETT STROSS (Stoke-on-Trent, Central, Lab.) urged that if a miner was disabled the onus of proof that he should not receive benefit should lie with the employer.

Universities and Colleges

UNIVERSITY OF OXFORD

In convocation on July 29 the honorary degree of D.Sc. was conferred on Professor J. B. S. Haldane, F.R.S., Honorary Fellow of New College.

In Congregation on July 29 the degree of B.M. was conferred on R. S. Cormack.

Professor P. B. Medawar, F.R.S., has been appointed to a Supernumerary Fellowship of St. Catherine's College, with effect from October 1, 1961.

UNIVERSITY OF LONDON

On June 21 the degree of M.D. was awarded by the Senate to D. F. Eastcott, P. D. Meers, F. Post, and M. H. P. Sayers.

In June the degree of Ph.D. in the Faculty of Medicine was awarded to Barbara M. Price (University of Leeds), M. V. Driver, M.B., B.S. (Institute of Psychiatry), and B. D. Vora (School of Pharmacy).

UNIVERSITY OF WALES

WELSH NATIONAL SCHOOL OF MEDICINE

In Congregation on July 21 the following degrees were conferred:

M.B., B.CH.—Hilda Bailey, V. A. Church, R. H. Clark, R. A. Cope, Deirdre J. Curran, D. M. Davies, H. S. Davies, J. S. Davies, Joan Evans.

R. W. Fortt, Nancy E. Francis, Alfred Kwong Chun Hui, P. D. L. John, D. J. Jones, Helen W. Jones, Margaret E. Jones, Anne M. Kriescher, D. G. Lewis, C. C. McCormick, Wing Shang Ng, D. K. Peters, Jean M. Peters, C. A. Quick, Jennifer H. Roberts, K. J. Russell, Patricia M. Wardlaw, J. G. Williams, N. B. Williams, A. C. MacD. Windsor, B. Wookey.

UNIVERSITY OF BRISTOL

Dr. T. F. Draisey, Dr. Sheila A. Faint, and Dr. D. Lamb have been appointed Demonstrators in Pathology.

Mr. E. M. Edwards, Lecturer in Obstetrics, and Dr. P. J. Roylance, Demonstrator in Anatomy, have resigned their appointments.

Vital Statistics

Shortage of Poliomyelitis Vaccine

The demand for poliomyelitis vaccination has been high this year. The Ministry of Health issued 11,500,000 doses in the first seven months against 8,750,000 doses in the whole of 1960. Unfortunately it has proved impossible to supply local authorities with all the vaccine they have asked for in August owing to the failure of two large batches to pass the Medical Research Council's tests for purity, potency, and safety, but it may be possible to make further issues later this month.

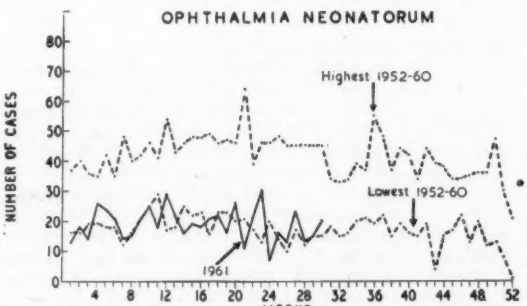
Infectious Diseases

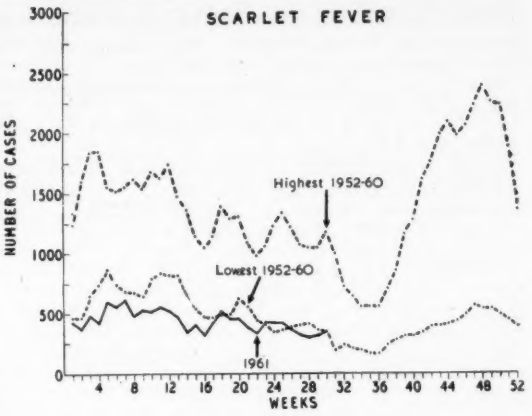
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

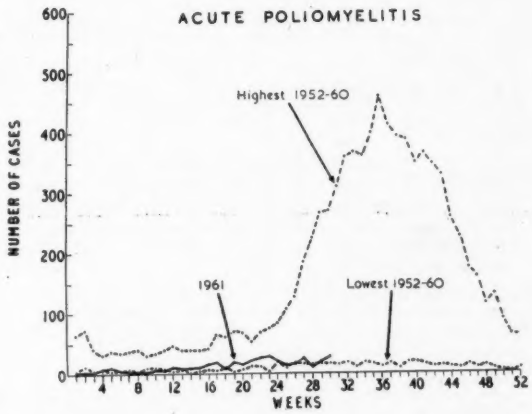
	Week Ending July 29	Week Ending Aug. 5
Measles		
Gloucestershire	403	**390**
Bristol C.B.	121	**111**
Lancashire	688	**584**
Liverpool C.B.	139	**135**
Yorkshire West Riding	917	**679**
Leeds C.B.	123	**108**
Dysentery		
Lancashire	91	**70**
Liverpool C.B.	14	**15**
London	63	**33**
Southwark	15	**19**
Yorkshire West Riding	69	**40**
Leeds C.B.	13	**15**
Sheffield C.B.	5	**10**

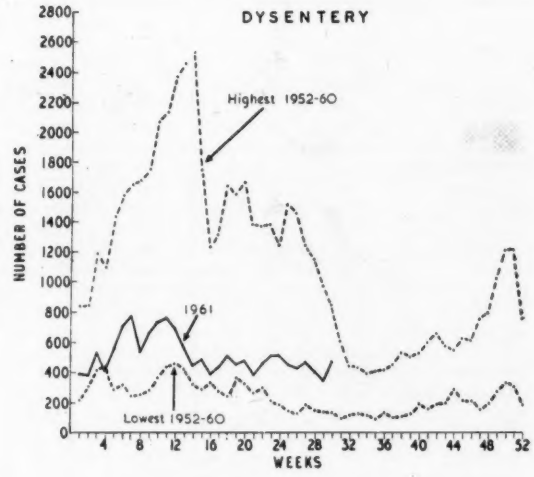
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Cholera in India and Sarawak

More than 3,500 people in Uttar Pradesh (formerly the United Provinces), India, have died in a cholera outbreak. About 13,000 cases have been notified up to July 15 (*The Times*, August 5, 1961). The World Health Organization has reported an outbreak of cholera in Sarawak and has arranged for supplies of vaccine to be flown to Kuching from India.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 29** (No. 30) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The tables is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	3	2	0	0	1	0	0	1	0	1
Dysentery	470	63	105		17	566	91	118	8	5
Encephalitis, acute	3	0		0		2	0		0	
Enteric fever:										
Typhoid	0	0	0	0		2	0	2	0	1
Paratyphoid	7	0	1(B)	1		12	5	4(B)	0	
Food-poisoning	206	49	24	0		222	31	57	2	
Infective enteritis or diarrhoea under 2 years				0	24				17	22
Measles*	9,958	190	54	198	159	2,856	139	66	2	4
Meningococcal infection	15	1	5	0		17	0	15	2	
Ophthalmia neonatorum	20	2	4	0		21	2	3	0	
Pneumonia†	139	8	105	3	1	131	5	96	0	
Poliomyelitis, acute:										
Paralytic	22	0	0	1	3	7	1	0	1	8
Non-paralytic	5	1	0			9	2	0		
Puerperal fever§	157	21	9	1		173	30	10	1	1
Scarlet fever	346	19	31	7	6	429	19	41	10	17
Tuberculosis:										
Respiratory	383	29	54	15		409	44	60	11	
Non-respiratory	52	2	8	2		65	6	12	0	
Whooping-cough	414	11	52	9	25	1,389	149	142	11	37

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	1		0		3	1		0	
Encephalitis, acute		0		0	0		0			0
Enteric fever	0	0	0			0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	0	0	1	9	0	1	0	1
Influenza	3	1	0	0	0	4	0	0	0	0
Measles		1	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	373	22	17	21	9	389	40	13	9	4
Poliomyelitis, acute	0	0		1	0	1	0		0	2
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	57	4	7	0	0	53	1	8	0	2
Non-respiratory		1			1		1	0	1	0
Whooping-cough	1	1	0	0	0	0	0	1	0	0
Deaths 0–1 year	308	40	21	9	23	308	27	22	7	16
Deaths (excluding stillbirths)	8,420	668	464	130	144	8,672	681	518	100	143
LIVE BIRTHS	15,725	1408	1032	268	457	15,832	1350	1014	298	503
STILLBIRTHS	280	23	19			288	29	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia

Medical News

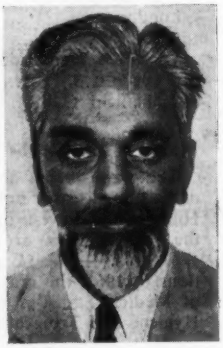
Dr. Lee's Chair of Anatomy, Oxford University

Professor G. W. HARRIS, F.R.S., Fitzmary professor of physiology at the University of London, has been appointed to the Dr. Lee's professorship of anatomy, University of Oxford, from October 1, 1962. He succeeds Sir WILFRID LE GROS CLARK, F.R.S., who has held the chair since 1934.

Professor Harris, who is 48, was educated at Dulwich College; University College, London University; Emmanuel College, Cambridge; and St. Mary's Hospital, London. From 1940 he was at Cambridge, lecturing successively in anatomy, then physiology, before becoming senior lecturer in physiology at London University in 1952. He was appointed to the Fitzmary professorship at the Institute of Psychiatry in the same year. He has been visiting professor at the universities of Montreal and California (Los Angeles and Berkeley) and lecturer at Johns Hopkins Hospital and at Massachusetts General Hospital. He was elected F.R.S. in 1953. His present research is largely concerned with studies on the control by the hypothalamus of the release of thyroid-stimulating hormone. He is also carrying out investigations into the isolation of the postulated neurotransmitter(s) concerned in the control of anterior pituitary function. He is the author of *Neural Control of the Pituitary Gland* (1955). The Swiss Society for Endocrinology has elected him to honorary membership.

Chair of Clinical Surgery, University College of West Indies

Mr. H. ANNAMUNTHODO, head of the department of surgery at the University College of the West Indies, Jamaica, has been appointed to the chair of clinical surgery there from October 1 in succession to Professor J. GILMOUR.



Mr. Annamunthodo, who is 41, qualified M.B., B.S. from the London Hospital Medical School in 1946, gained the D.T.M.&H. in 1947, was elected F.R.C.S.(Eng.) in 1951, and F.A.C.S. in 1960. His last appointment in the United Kingdom was as senior surgical registrar, King George Hospital, Ilford, from 1950 to 1953. He was lecturer and then senior lecturer at the University College of the West Indies from 1957 to 1961. He was a Rockefeller Foundation Fellow at Yale University from 1959 to 1960, and Hunterian Professor, Royal College of Surgeons, in 1960.

Colonial Development and Welfare Schemes

Last year the United Kingdom spent the record sum of nearly £26m. on development and welfare schemes for her overseas territories. This included £1,503,637 for medical and health services, £1,004,962 for developing water supplies and sanitation, £400,624 for medical research, and £223,784 for tsetse and trypanosomiasis research. Since 1946 £254,520,198 has been spent in grants and loans for development and welfare schemes, the largest sum (£46,152,666) going to roads, followed by £31,807,288 to agriculture and veterinary schemes, £25,128,895 to primary and secondary education, £22,423,349 to medical and health services, and £20,408,689 to water supplies and sanitation. (*Return of Schemes, Colonial Development and Welfare Act*, H.M.S.O., price 3s. 6d. net.)

International Federation of Surgical Colleges

The executive committee of the International Federation met recently in Paris, with the President, Sir HARRY PLATT, in the chair. Two new members were reported—the Association Française de Chirurgie and the Japanese Surgical Society. The 1961 meeting of the International Federation is to be held in Oslo, September 12–14. The theme will be "Surgical Research." The President and Professor CARL SEMB and the Secretary reported on a meeting held on May 17 in Geneva with representatives of the World Health Organization and League of Red Cross Societies on the subject of surgical aid in military and civil emergencies and educational missions. It was decided that certain recommendations would be made to the Council about liaison between surgical colleges and national Red Cross Societies. The committee received with great satisfaction a report on the visit of Mr. NORMAN MATHESON to the Shiraz Medical Centre, Iraq. This visit had been arranged by the International Federation in answer to a request from Dr. R. A. WISE, visiting professor and director of surgical studies in Shiraz University, and had been made possible by a grant from the British Council. Mr. Matheson had also visited Bagdad, Basrah, and Meshed, where he had conducted clinical demonstrations, lectures, and operations. A vote of thanks was given to Professor J.-L. LORTAT-JACOB for his hospitality to the members of the Committee and for obtaining the use of the Foyer des Professeurs of the Faculty of Medicine for the meeting.

British Association of Paediatric Surgeons

The secretariat of the British Association of Paediatric Surgeons is no longer at the Hospital for Sick Children, Great Ormond Street, but at Alder Hey Children's Hospital, Liverpool 12, to which any correspondence should be sent.

Opportunities in Antarctica

Every year there are two or three vacancies for medical officers at the bases maintained by the Falkland Islands Dependencies Survey which operates in the British Sector of the Antarctic continent. The character of the bases varies to some extent depending upon their situation and *raison d'être*, but ski-ing and dog-sledging are common to all. Medical research is actively encouraged, and in recent years

Sledging on sea ice south of Hope Bay, Graham Land.

several theses from F.I.D.S. medical officers have been accepted for higher degrees. Doctors are normally accepted for a period overseas of about 18 months, and whenever possible in allocating medical officers to bases individual preferences for field-work, biology, and physiology are taken into account. On the voyage to the Antarctic the ships call at South America and the Falkland Islands. Pay depends upon qualification and experience, and special consideration will be given to applicants with domestic responsibilities. While overseas, salaries are subject to Falkland Islands income tax, and it is easily possible to save over £600 after one season. Paid leave is earned at the rate of three days for every month spent outside the United Kingdom. Grants are available for periods up to two years for medical officers to organize and write up research projects. Arrangements will be made for suitable candidates to meet a doctor who has done a term "down south," and interested applicants should write to: Sir VIVIAN FUCHS, c/o F.I.D.S., Crown Agents, Millbank, London S.W.1.

Royal Commonwealth Society for the Blind

The Royal Commonwealth Society for the Blind announces in its *Annual Report 1960–61* that as knowledge of its work grows increasing support is coming from the public. The Society's work is steadily developing: new schools and training centres are being built or planned in many places. Substantial progress has been made in many territories towards achieving comprehensive systems of blind welfare. Ever-increasing attention is being paid to the urgent need for more medical and surgical help in combating blindness. Above all, public opinion throughout the Commonwealth is becoming aware of the magnitude of the task that faces it—in Southern Rhodesia alone, for example, 892 of every 100,000 people are blind. Generous grants have been made to the Commonwealth Scholarship Fund by the Royal National Institute for the Blind and the Canadian National Institute for the Blind. The Fund has assisted 26 people, including four doctors who have received scholarships to enable them to take the Diploma in Ophthalmology. The Society would welcome more applications to this Fund and support for the scheme generally. Its address is 46 Victoria Street, London S.W.1.

College of G.P.s' Medical Recording Service

Recordings on tape and disk from the Medical Recording Service's Sound Library may now be borrowed by any doctor whether or not he is a member of the College. Recent titles include: "Speech Disorder in Neurological Disease" (with 15 recordings of typical voices), by Dr. E. C. O. JEWESBURY; "Anticoagulants," by Sir JOHN RICHARDSON; "The Treatment of Parkinsonism," by Dr. M. J. PARSONAGE; "The Alcoholic can be Cured," by Dr. N. H. RATHOD and "Vera," who was an alcoholic patient. For details and a library list apply to the College of General Practitioners, 41 Cadogan Gardens, Sloane Square, London S.W.3. The work of the Medical Recording Service was described in the *B.M.J.*, September 6, 1958, p. 583, and May 21, 1960, p. 1580.

Stepping Stones House

The department of psychiatry at Bromley Hospital, Kent, has issued its first report on Stepping Stones House, a building housing the psychiatric out-patient clinic and the Stepping Stones Club. The house was purchased, converted, furnished, and equipped out of a grant of £17,000 made by the King Edward's Hospital Fund for London and was opened in 1957. The club offers many forms of group activity to mentally ill patients—from silk-screen printing and carpentry to work in the canteen—and local voluntary helpers enjoy equal status with them as members. As far as possible neither patients nor helpers are allowed to know which club members are patients and which are helpers. The club is believed to be unique in this respect, and its organization reflects changes that have taken place of recent years in the practice of psychiatry and in the attitude of the community to mental health. The Bromley Group Hospital Management Committee finances the maintenance of Stepping Stones House, and the club enjoys the support of the local community and of the Friends of Bromley Hospital.

New Hospital for Shetlands

On August 8 QUEEN ELIZABETH THE QUEEN MOTHER opened the new £410,000 Gilbert Bain Hospital at Lerwick in the Shetlands. It has 62 medical and surgical beds, and the adjacent isolation hospital has been converted into a maternity unit with 11 beds. All windows are double glazed because of the high winds, and on each of the two ward floors there is a day room commanding a magnificent view of Brei Wick Bay and the neighbouring islands.

Storage and Disposal of Agricultural Chemicals

The Ministry of Agriculture, Fisheries and Food has warned farmers that partly used containers of poisonous chemicals can be dangerous to people, livestock, domestic fowls, and wild life unless they are properly stored or disposed of safely. Advice on how this can be done can be obtained at any Divisional Office of the Ministry of Agriculture, Fisheries and Food.

In Brief

The London Clinic has submitted an outline planning application to the London County Council for building a new wing to increase accommodation for patients and staff, and to house the pathology, radiology, radiotherapy, and physiotherapy departments.

People in the News

▶ Dr. J. H. F. JAYASURIYA, chairman of the Council of the Ceylon National Association for the Prevention of Tuberculosis, has been awarded the Commonwealth Award of Honour of the National Association for the Prevention of Tuberculosis of Great Britain and Ireland for "meritorious voluntary service in the fight against tuberculosis."

▶ Mr. J. B. JOHNSTON, who was senior surgical registrar at the Brompton Hospital, London, has been appointed associate professor of cardiopulmonary surgery in the University of New South Wales. (*Med. J. Aust.*, July 15.)

▶ Mr. G. F. MURNAGHAN, formerly Scottish Hospitals Endowments Research Trust Fellow in urology and honorary senior registrar in urology at the Western General Hospital, Edinburgh, has been appointed associate professor of urological surgery in the University of New South Wales. (*Med. J. Aust.*, July 15.)

▶ Dr. P. W. NATHAN, of the Neurological Research Unit, Medical Research Council, National Hospital, Queen Square, is to be visiting professor of neurology at Denver, Colorado, for six months from the end of August.

▶ Sir HARRY PLATT will visit Australia and New Zealand in November and December at the invitation of the Royal Australasian College of Surgeons. When in Melbourne he will take part in the ceremonies connected with the launching of an appeal by the College for funds to support and extend its postgraduate activities.

COMING EVENTS

7th International Congress of Permanent Section on Biological Standardization of International Association of Microbiological Societies.—London, August 28–September 1, Wellcome Foundation, Wellcome Building, Euston Road, London N.W.1. Chairman: Professor A. A. MILES, F.R.S.

19th Congress of International Society of Surgery.—Dublin, September 2–9 (President: Professor E. DAHL-IVERSEN, Copenhagen). First two days devoted to discussion, "Surgery of the Endocrine Glands," then clinical papers of general interest, experimental surgery, and forum for shorter communications. Congress joined on September 7 by International Cardiovascular Society (President: Professor CHARLES ROB, Rochester, New York). Grey-Turner Memorial Lecture: Professor LAMBERT ROGERS, September 7, 3 p.m. Details of congress from Mr. H. W. S. WRIGHT, 9 Weymouth Street, London W.1, or Professor LAMBERT ROGERS, Royal Infirmary, Cardiff.

London University Union Socialist Society Medical Group.—Meeting to discuss formation of group, September 5, 7.30 p.m., University of London Union, Malet Street, London W.C.1.

7th International Convention on Vital Substances, Nutrition, Civilization Diseases.—Aachen, Liège, Maastricht, September 12–17. Details from Secretary, 61 Bemeroder Strasse, Hanover-Kirchrode, Germany.

Harveian Library.—Exhibition, "Some Anniversaries of 1961," may be viewed on consultation with Librarian, Royal College of Physicians of London, Pall Mall East, London S.W.1. (Tel.: WHitehall 7701.)

3rd International Conference on Alcohol and Road Traffic.—London, September 3–7, 1962, B.M.A. House. Tavistock Square, London W.C.1. Patron H.R.H. the DUKE OF EDINBURGH. President: Minister of Transport, Mr. E. MARPLES. Details from Conference Secretary, Dr. J. D. J. HAVARD, at B.M.A. House.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

JOURNAL OF CLINICAL PATHOLOGY

Studies on the Folic Acid Activity of Human Serum. A. H. Waters and D. L. Mollin.
Conventional Voltage Electrophoresis for Formiminoglutamic Acid Determination in Folic Acid Deficiency. J. Kohn, D. L. Mollin, and L. M. Rosenbach.
The Urinary Excretion of Assayable Vitamin B_{12} and Radioactivity After Parenteral ^{58}Co B_{12} in Man. J. F. Adams.
A Suggested Schedule for the Rapid Investigation of Acute Haemostatic Failure. G. I. C. Ingram.
Studies on the Blood Lipids and Lipoproteins in the Thalassaemia and Sickle Cell Anaemia. C. Choremis, V. Kyriakidès, and E. Papadakis.
Hereditary Elliptocytosis in Two Maltese Families. J. L. Grech, E. A. Cachia, F. Calleja, and F. Pullicino.
The Significance of Howell-Jolly Bodies and Giant Metamyelocytes in Marrow Smears. D. W. Dawson and H. P. R. Bury.
The Rate of Blood Loss from Skin Punctures During the Ivy Bleeding Time Test. M. L. N. Willoughby and M. J. Allington.
Methicillin-resistant Staphylococci. Mary Barber.
Coccidiosis in Guinea-pigs. P. A. Ellis and A. E. Wright.
Rapid Isolation of Salmonellae from Faeces. J. M. S. Dixon.
The Estimation of Magnesium in Small Biological Samples by Flame Spectrophotometry. R. D. Montgomery.
The Determination of Magnesium in Biological Materials by Flame Photometry. J. K. Fawcett and V. Wynn.
Plasma Magnesium in Health and Disease. Samir Hanna.
A Possible Source of Error in the Diagnosis of Phaeochromocytoma. D. W. Neill, I. J. Carré, R. L. McCorry, and R. H. Thompson.
A Sensitive Method for the Colorimetric Determination of Urea. R. N. Beale and D. Crott.
The Use of Tetramethylammonium Hydroxide in the Zimmermann Reaction. V. H. T. James and Mary de Jong.
Laboratory Studies with the Systemic Trichomonacide, Metronidazole. R. F. Jennison, P. Stenton, and Leslie Watt.
Paper Tests for Occult Blood in Faeces and Some Observations on the Fate of Swallowed Red Cells. R. G. Huntsman and J. Liddell.
Technical Methods:
Quantitative Determination of A2 Haemoglobin by Paper Electrophoresis Using Tris Buffer. R. T. S. Jim.
A Method of Rapid Rh Typing Employing the Capillary Tube Technique and Papainized Incomplete Anti-D Sera. B. E. Gilbey.
The Rapid Slide Agglutination Test in the Diagnosis of Typhoid Fevers and Typhus. B. Z. Werbin and A. Kasher.
Haemoglobinometry by an Automatic Analytical Procedure. M. G. Nelson and A. Lamont.
Improvement of the Uric Acid Determination by the Carbonate Method for Serum and Urine. F. Eichhorn, S. Zelmanowski, E. Lew, A. Rutenberg, and B. Fanias.
Book Reviews.

Volume 14, No. 4. (Bi-monthly; £4 4s. annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, August 22

LONDON UNIVERSITY.—At London Hospital Medical College, 5 p.m., Professor G. de Takats (University of Illinois): Intermittent Claudication.
ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Dr. J. C. Beck (Montreal): Metabolic Effects of Growth Hormone in Man.

Wednesday, August 23

ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Dr. A. G. Bearn (New York): Genetics in Clinical Medicine.

Friday, August 25

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Howard Nicholson: clinical demonstration.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Boak.—On June 21, 1961, at Buchanan Hospital, St. Leonards on Sea, to Alison (formerly Francis) and Dr. J. L. Boak, a daughter—Jane.
Craig.—On August 8, 1961, at Bristol Maternity Hospital, to Patricia (formerly O'Sullivan), M.B., and Kevin Craig, F.R.C.S., a daughter—Josephine.

DEATHS

Carpenter.—On July 23, 1961, at his home, James Edwin Carpenter, *M.C.*, M.R.C.S., L.R.C.P., of Westcliff-on-Sea, Essex.
Dawson.—On July 21, 1961, at his home, 8 Sefton Drive, Wilmslow, Cheshire, George Duncan Dawson, M.D., D.P.H., aged 78.
Fagge.—On July 25, 1961, Charles Hilton Fagge, B.M., B.Ch., of Blandford House, Braintree, Essex.
Wallace.—On July 8, 1961, at his home, Brisbane, Queensland, Australia, Thomas Irby Wallace, M.B., Ch.B., formerly of Glasgow, aged 80.
Whitsitt.—On July 11, 1961, in London, Leslie Montgomery Whitsitt, M.B., B.Ch.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Second Attack of Poliomyelitis

Q.—*A child aged 20 months recently had an attack of poliomyelitis which was reported to be due to type 1 virus. He now has some residual weakness of his left leg. Would you advise immunizing the child against the other types of poliomyelitis virus? If so, how long after the onset of the illness should this be performed?*

A.—The only possible procedure in this country is to give a full course (three or four doses) of ordinary (multivalent) inactivated Salk-type vaccine; there is no need to differentiate between the serological types or to consider giving only types 2 and 3. (If oral live virus vaccines of different types were available protection against types 2 and 3 only could probably be achieved.) A second attack of polio with the same serological type has not been recorded; a second attack with another type does occur but is rare. The vaccine could be given forthwith, without regard to a definite time-interval from the illness.

Ultra-violet Light for Chilblains

Q.—*It was stated in "Any Questions?"[1] that protection from chilblains can be obtained by exposure to ultra-violet light at the beginning of the autumn. Should this exposure be local or general, and on what evidence is the statement based?*

A.—Exposure to ultra-violet radiation in erythema dosage for chilblains should be local. In perniosis the smaller arterioles go into spasm readily from exposure to cold. The injury reaction from the erythema produced by ultra-violet radiation causes a relaxation of these vessels which persists for a considerable period.[2]

REFERENCES

1 *Brit. med. J.*, 1961, **1**, 1477.
2 Holti, G., *Clin. Sci.*, 1955, **14**, 137 and 143.

Separate Syringes

Q.—*Local authorities issue polio vaccine in 10-ml. phials. Is it justifiable to give a series of immunizations from a filled 10-ml. syringe—changing the needle between each patient—or does this involve a risk of transmitting infective hepatitis?*

A.—If the virus of serum hepatitis can travel back through the needle into the syringe then hepatitis can be transmitted to the next patient injected by that syringe. It obviously does not matter whether the syringe is a 1-ml. syringe or a 10-ml. syringe, and changing the needle each time is no safeguard. The risk of transmitting the disease is, of course, greatest in intravenous injections but cannot be excluded in subcutaneous injections, and cases of serum hepatitis have been traced to the procedure described in the question. A separate syringe and needle for each injection is the only complete defence.

Protection Against Dyestuffs

Q.—*How do the industrial dyestuffs which cause urinary-tract tumours get into the blood-stream? Is there any danger in using these dyes in art colleges where fabric printing is done?*

A.—The substances which have been found responsible for occupational tumours of the urinary tract enter the blood-stream by inhalation, ingestion, and absorption through the intact skin. Such occupational cases have followed exposure during the manufacture of dyestuff intermediates[1] and there is no definite evidence of any hazard from the use of the finished dyes.[2] Nevertheless, if they are being used in such a way that the skin or clothing can be grossly contaminated, a high standard of personal hygiene should be maintained, including the wearing of protective clothing (especially gloves of rubber or polythene) frequently changed and washed. A thorough bath should be taken immediately and fresh clothing put on if accidental contamination should occur.[3]

REFERENCES

1 Goldblatt, M. W., and Goldblatt, J., *Industrial Medicine and Hygiene*, Vol. 3, 1956. Butterworth, London.
2 Poole-Wilson, D. S., *Proc. roy. Soc. Med.*, 1960, **53**, 801.
3 Scott, T. S., and Williams, M. H. C., *Brit. J. industr. Med.*, 1957, **14**, 150.

Antihistamines in Recurrent Urticaria

Q.—*Do oral antihistamines relieve recurrent urticaria of unknown aetiology when elimination diets and skin tests have been of no real value?*

A.—Oral antihistamines give considerable help in mild cases of recurrent urticaria of unknown aetiology. Skin tests are rarely of value in cases of urticaria.

Volatile Substances in Cigarette Smoke

Q.—*What are the volatile substances in cigarette smoke, and which of them are carcinogenic? In what liquids are they soluble?*

A.—Cigarette smoke is known to contain some hundreds of different substances. In addition to nicotine there are many other bases. There are also acids, phenols, hydrocarbons, neutral organic compounds, and even some inorganic material. Most of the constituents of cigarette smoke have not been tested for carcinogenic activity. The hydrocarbon fraction does, however, contain small amounts of 3:4-benzpyrene, which is known to be carcinogenic.

Many of the constituents of tobacco smoke are soluble in water, but fresh tobacco smoke is completely soluble in organic solvents such as acetone or alcohol. There is a short list of tobacco constituents in a paper by A. I. Kosak.[1]

REFERENCE

1 Kosak, A. I., *Experientia*, 1954, **10**, 69.

Von Mikulicz's Disease

Q.—*Is there any treatment in a case of von Mikulicz's disease involving both submandibular glands only? Peripheral blood count is normal and no other glands are involved. In particular, is there any mouth wash or lozenge that can relieve the associated xerostomia?*

A.—Mikulicz's disease is rare, and as in this case only the submandibular salivary glands are affected the diagnosis should not be made until many other conditions have been excluded. Since the greater part of the total buccal saliva is secreted by the parotid glands, it is most unlikely that the xerostomia is the result of disease affecting only the submandibular glands, and a marked degree of dryness suggests involvement of several of the larger glands, including one or both parotids. Did the xerostomia precede the enlargement of the submandibular glands, and are the enlargements asymptomatic or periodic?

In all but the most straightforward diseases of the salivary glands the questions have to be asked whether the disease is a primary one; whether it is secondary to some other local condition; or whether it is a manifestation of a systemic process. For example, a recurrent or chronic bacterial infection, usually due to a *Streptococcus viridans*, may involve several glands but show definite signs in only one or two, yet such a condition may occasionally be the first manifestation of a leukaemic process or of lupus erythematosus.

This patient, therefore, should be fully investigated before being labelled or treated as a case of Mikulicz's disease. These investigations must include skiagrams of all the salivary glands, the examination and bacteriology of a catheter

specimen of saliva from one or more of the glands, sialograms of one or two of the glands, as well as a full systemic investigation to include blood cytology and chemistry.

Accurate diagnosis may allow treatment to be carried out which will restore salivary function. Symptomatic relief may be given by the frequent taking of watery drinks and by the use of a mucin spray.

Risks of Prolonged Stilboestrol Therapy

Q.—*Is there any risk of cancer in a patient who has been taking stilboestrol for a period of about five years for menopausal symptoms? She still gets hot flushes when it is stopped, but while taking it is entirely symptom-free.*

A.—It has never been established that oestrogens given in prolonged and heavy dosage cause the development of cancer in the human being. Nevertheless, it is a theoretical possibility which cannot be ignored, especially in regard to carcinoma of the uterus. It is of some importance to know what dose of stilboestrol is being used in this case, and whether the woman has been subjected to hysterectomy. If the uterus has not been removed then, irrespective of the possibility of malignant change, the problems of endometrial hyperplasia and post-menopausal bleeding may arise.

There is, in any case, little justification for continuing the administration of stilboestrol for five years. It will never cure hot flushes, and the longer it is continued the more severe are likely to be the effects of its withdrawal. The only object of oestrogen therapy for menopausal symptoms is to permit a gradual reduction of an oestrogen influence, and ordinarily a course of treatment is completed within a few months.

In this case it should be explained to the patient that, apart from any ill effect which it may have, the continued taking of stilboestrol is only "postponing the evil day." She should be persuaded to reduce the dose gradually over the course of two or three months and to adhere to a strict dosage plan despite the inevitable occurrence of some flushes both during and after the weaning process.

Smallpox Vaccination and Eczema

Q.—*A child aged 7, who has suffered from eczema since birth, is now living in East Africa, and should be vaccinated against smallpox. What precautions can be taken to prevent a secondary viral infection or aggravating the eczema? Would a "blanket" course of cortisone be advisable, or would this interfere with the degree of immunity conferred by the vaccine and nullify its action?*

A.—If vaccination is imperative, it would be desirable to clear the eczema first if possible. A dry climate in the hills rather than a hot, humid atmosphere might help in this, together with antihistamines, such as trimeprazine, internally, and hydrocortisone applications on face and neck, and "coltapaste" bandages, undisturbed, on the limbs. There would be no objection to cortisone, if necessary, on a short-term basis. When vaccination is performed it would be wise to cover the site with an occlusive zinc paste dressing and keep it covered for a fortnight. Cortisone would not interfere with the degree of immunity conferred.

Lapse in Poliomyelitis Immunization Course

Q.—*What procedure should be adopted in children who had their first two doses of poliomyelitis vaccine two years ago but failed to attend for further injections? Should they begin again and have the recommended full immunization course of injections?*

A.—Although considerable individual variation in their circulating antibody titres would be expected, all such children may be considered to have a reasonable basal immunity and to respond well to further stimuli. One reinforcing dose of inactivated vaccine might suffice, but it would be preferable to begin again in order to ensure the better protection of the poor responders. Two doses, spaced by 4 to 6 weeks, should be given and a further dose after a long interval—say in the spring of next year. A good reason for this thoroughness is that the inactivated vaccines of a few years ago tended to be less potent than those in current use.

Glycosuria in Elderly Diabetics

Q.—*Is 0.5–1% of sugar in the urine reasonable and harmless in a diabetic aged 70 who is dieting only, and has no appreciable symptoms at all?*

A.—Glycosuria of this extent in a diabetic aged 70 can be safely disregarded, provided there is no ketonuria or impairment of renal function.

Fitness for Underwater Swimming

Q.—*I have been asked by a patient to provide a certificate for his club to say he is fit for underwater swimming (aqualung). Are there any recognized standards for this?*

A.—The British Sub-Aqua Club has its own form which all new applicants to join have to get filled up, at their own expense, to show that they are medically fit for diving. Many useful hints on the physiology of diving and the training schedules of the club are to be found in volume 2 of its *Training Manual* (obtainable from B.S.A.C. Agent, 25 Orchard Road, Kingston upon Thames, Surrey). Any history of syncopal attacks, whether vasomotor in origin or of a petit mal type, must permanently preclude diving. A recent miniature radiograph (within twelve months) to exclude phthisis or obvious emphysematous bullae is also insisted upon. Any angina of effort in those over the age of 45 or known claustrophobia would also suggest care. The last obvious necessities are absence of external auditory wax, intact tympanic membranes, and an ability to insufflate the Eustachian tubes.

An article on a pressure hazard of diving appears at p. 483 of this issue.

Withdrawal Symptoms in Chlorodyne Addiction

Q.—*Have convulsions been known to occur when withdrawing chlorodyne from patients who are addicted to it?*

A.—Fits have been observed to occur in patients from whom chlorodyne is being withdrawn; this was, however, in association with withdrawal of barbiturates also. One would not expect fits on withdrawal of chlorodyne alone, but would not say that such an occurrence was impossible.

Correction.—The year of birth of the late Professor R. M. Gordon should have been given in the obituary notice in the *Journal* of August 5 (p. 387) as 1893, not 1898.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Any Questions?, Volume 3 (8s. 3d.).

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7 Drumsheugh Gardens, Edinburgh.